



THE
GREAT
COURSES®

Topic
Better Living

Subtopic
Health & Wellness

Stress and Your Body

Course Guidebook

Professor Robert Sapolsky
Stanford University



PUBLISHED BY:

THE GREAT COURSES

Corporate Headquarters

4840 Westfields Boulevard, Suite 500

Chantilly, Virginia 20151-2299

Phone: 1-800-832-2412

Fax: 703-378-3819

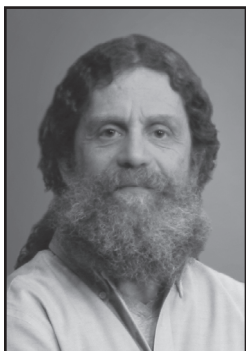
www.thegreatcourses.com

Copyright © The Teaching Company, 2010

Printed in the United States of America

This book is in copyright. All rights reserved.

Without limiting the rights under copyright reserved above,
no part of this publication may be reproduced, stored in
or introduced into a retrieval system, or transmitted,
in any form, or by any means
(electronic, mechanical, photocopying, recording, or otherwise),
without the prior written permission of
The Teaching Company.



Robert Sapolsky, Ph.D.

Professor of Neurology and Neurosurgery
Stanford University

Robert Sapolsky holds the John A. and Cynthia Fry Gunn Professorship of Biological Sciences at Stanford University, where he is also Professor of Neurology and Neurosurgery. Professor Sapolsky's laboratory focuses on the mechanisms by which stress and stress hormones can damage the brain and on the

development of gene therapy strategies to save neurons from neurological insults. In addition, he has spent most of his summers since the late 1970s studying a population of wild baboons in East Africa, examining what social rank, personality, and patterns of sociality have to do with vulnerability to stress-related diseases.

Professor Sapolsky has been the recipient of many awards for his work, including a 2009 Walter J. Gores Award for Excellence in Teaching, Stanford University's highest teaching honor.

Professor Sapolsky writes regularly for nonscientists in such publications as *Scientific American*, *Discover*, *Natural History*, and *The New Yorker*. He is also the author of 5 books, including 4 nontechnical publications for the general public: *Why Zebras Don't Get Ulcers: A Guide to Stress, Stress-Related Diseases, and Coping* (3rd edition, Henry Holt, 2004); *The Trouble with Testosterone and Other Essays on the Biology of the Human Predicament* (Scribner, 1997); *A Primate's Memoir* (Scribner, 2001); and *Monkeyluv and Other Essays on Our Lives as Animals* (Scribner, 2005). ■

Table of Contents

INTRODUCTION

Professor Biography	i
Course Scope	1

LECTURE GUIDES

LECTURE 1

Why Don't Zebras Get Ulcers? Why Do We?	4
---	---

LECTURE 2

The Nuts and Bolts of the Stress-Response	7
---	---

LECTURE 3

Stress and Your Heart	12
-----------------------------	----

LECTURE 4

Stress, Metabolism, and Liquidating Your Assets	15
---	----

LECTURE 5

Stress, Overeating, and Your Digestive Tract	18
--	----

LECTURE 6

Stress and Growth—Echoes from the Womb	21
--	----

LECTURE 7

Stress, Growth, and Child Development	25
---	----

LECTURE 8

Stress and Female Reproduction	28
--------------------------------------	----

LECTURE 9

Stress and Male Reproduction	32
------------------------------------	----

LECTURE 10

Stress and Your Immune System	35
-------------------------------------	----

Table of Contents

LECTURE 11	
Stress and Cancer	39
LECTURE 12	
Stress and Pain	43
LECTURE 13	
Stress, Learning, and Memory	46
LECTURE 14	
Stress, Judgment, and Impulse Control	49
LECTURE 15	
Stress, Sleep, and Lack of Sleep	52
LECTURE 16	
Stress and Aging	55
LECTURE 17	
Understanding Psychological Stress	58
LECTURE 18	
Psychological Modulators of Stress.....	61
LECTURE 19	
Stress and the Biology of Depression	64
LECTURE 20	
Stress and the Psychology of Depression.....	68
LECTURE 21	
Anxiety, Hostility, Repression, and Reward	71
LECTURE 22	
Stress, Health, and Low Social Status	75
LECTURE 23	
Stress Management—Clues to Success?	78

Table of Contents

LECTURE 24

Stress Management—Approaches and Cautions	81
---	----

SUPPLEMENTAL MATERIAL

Glossary	84
Bibliography.....	91

Stress and Your Body

Scope:

Few people taking this course are likely to be lepers, have liver flukes, or suffer from malaria. Few will have lost their mothers to childbirth or be malnourished. Westernized humans are unlike other animals because we are spared the classic infectious diseases, undernutrition, and poor hygiene. Instead, we live well enough and long enough that our serious diseases are ones of slow accumulation of damage, such as heart disease, diabetes, and cancer.

These are unique ways of getting sick. Imagine a person 20,000 years ago accidentally eating a bushbuck riddled with anthrax. The prognosis is clear—he has about a 3-day life expectancy. Imagine a contemporary person accidentally deciding that a healthy diet consists of lots of red meat, saturated fats, and a few drinks each day. The prognosis is not at all clear—she could be dead at 50 or running marathons at 85. Some of that variability arises from nuts-and-bolts biology, such as, how does her liver deal with cholesterol? But some has to do with issues never before seen as relevant to medicine, issues that generate bizarre questions such as, what is her psychological makeup? What is her social status? How do people of that status get treated in her society? Even things like is she the sort of person who eats a lot more when she is feeling worried or unloved? This is a strange realm for making sense of who is healthy and who gets sick. And it is critical to note that most of these diseases of slow degeneration and Westernized lifestyle can be caused or worsened by stress. Most of us will have the luxury of dying of a stress-related disease.

Nonetheless, we can try to delay that from happening. To hark back to a term from 9th grade biology, our bodies seek homeostasis, the state where there is an ideal blood pressure, temperature, level of glucose in the bloodstream, and so on. A stressor can be defined as anything in the outside world that disrupts homeostatic balance. Consider a zebra that has been attacked by a lion, with its innards dragging in the dust, still needing to flee. I think it is fair to state that this counts as being out of homeostatic balance. Or consider

that lion, half-starved, who must find the energy to run down a prey and survive. In both of those animals, there is activation of the stress-response (involving, among other things, the secretion of epinephrine). And that response is highly adaptive under those circumstances. The stress-response diverts energy from storage sites throughout the body to exercising muscle. Blood pressure, heart rate, and breathing rate increase, accelerating delivery of nutrients to where they're needed—get that oxygen and glucose to the thigh muscles in 2 seconds instead of 3, and the animal is more likely to survive. Long-term, costly building projects throughout the body—such as growth, tissue repair, reproduction, and digestion—are inhibited. If an animal is running for its life, it's not a bad idea to ovulate some other time; it can do it later, if there is a later. Its pain perception is blunted, its body gets better at clotting a wound, its immune system activates, and its brain is alert and processing information more acutely. This is all highly adaptive.



© Hemera/Thinkstock

Zebras and other animals activate their stress-response only when necessary.

Then there are humans. We activate the stress-response if being chased by a predator. But, critically, we can activate that same response if we merely think we're about to be knocked out of balance—we have an anticipatory stress-response. If it is justified, that is a great thing. But if there is no actual physical stressor impending, and we do that regularly, we have entered the realm of anxiety, neurosis, hostility, and paranoia. Zebras do not worry about global warming, but we do. We activate the identical stress-response as do zebras and lions, but we can do so because of chronic psychological stress. And if that occurs often enough, our disease risk increases, because that is not what the stress-response evolved for. This is the central point of this course.

Chronically diverting energy from storage sites increases the risk of metabolic diseases such as diabetes. Chronically increasing blood pressure or deferring growth, tissue repair, or reproduction can exact a health price. In contrast to the situation with acute stress, chronic stress suppresses, rather than stimulates, the immune system, increasing risk for infectious diseases. And chronically activating the stress-response can cause memory problems, increase the risk of depression and anxiety disorders, and even accelerate brain aging. In other words, we humans are smart enough to make ourselves sick with thoughts, emotions, and memories—and we Westernized humans live long enough for the consequences to eventually haunt us big-time.

The first part of the course marches through various parts of the body (e.g., heart, stomach wall, and immune system) or physiological functions (e.g., sleep, learning, and memory), examining first what happens during the sort of stress experienced by a zebra or lion—how that is great adaptive news for them—and then, for each of those systems, how chronic stress winds up being bad news for us. The information is presented at the level of an educated individual who, nonetheless, hasn't gone near science since high school. The course then examines what it is that makes psychological stress stressful, and its relevance to depression, anxiety, and addiction. We examine the role of personality differences in explaining why some individuals cope with stress better than others, and we explore what socioeconomic status has to do with stress and health. By this point in the course, you should be depressed as heck. The final 2 lectures are an overview of stress management: Remarkably, there are reasons for optimism. ■

Why Don't Zebras Get Ulcers? Why Do We?

Lecture 1

Sit down a hippo and try to explain traffic jams, and it's going to have no idea what you're talking about. We do, though, and that's the critical point of the whole field of stress and disease. We turn on the exact same stress-response as do those mammals running for their lives or running for a meal, and we turn it on for psychological reasons.

When most of the beasts on this planet become sick, it is due to acute crises. You are a zebra, and a lion has leapt out and ripped your stomach open. Your innards are dragging in the dust, and you still need to get out of there. Or you're the lion who's half starved to death, and if you don't manage to chase down that zebra, you're not going to survive the night. You have been knocked out of homeostatic balance. Short-term physical crisis leads to the **stress-response**: You secrete adrenalin and other hormones to reestablish **homeostasis**. If you're a zebra or a lion, that's all you need to know about the subject.

What do we humans, especially Westernized humans, do instead? We worry about physiological states. We worry about our body slowly being done in by things like heart disease and stroke. In lots of ways, the

central question in Westernized disease these days is why do some of us live to 50 and some of us to 85? Some of that has to do with biology, but a lot of it has to do with issues like social status and psychological makeup. When you look at the diseases that get us sick these days, those diseases of slow accumulation over time, they are predominantly diseases that are sensitive



© iStockphoto/Thinkstock

The stress-response is a good thing for animals in the wild, such as zebras attacked by a lion.

to stress. Most of us will have the profound Westernized luxury of dropping dead someday of a stress-related disease.

How does stress impact our lives? How does stress impact our health? Not just any kind of stress: the psychological and psychosocial stress that we

We humans activate the stress-response for reasons of psychological factors, and that's simply not what the system evolved for.

Westernized humans specialize in. If you're a human, yes, stress can be when you're knocked out of homeostatic balance. But a **stressor** can also be when you think you're about to be knocked out of homeostatic balance. If you think you're about to be knocked out of homeostatic balance, and you're really not, and you think that way all the time, there are medical ways to describe you: You're being neurotic, anxious, paranoid, or hostile.

We humans activate the stress-response for reasons of psychological factors, and that's simply not what the system evolved for. If you do that chronically, you're going to get sick. The

problem is that after a while, your stress-response is more damaging than the stressor itself, especially if the stressor was some psychological nonsense you made up. Everything you're doing with your body here is inefficient, but you got to do it because today is an emergency. If for psychological reasons, every day is an emergency, you never fix, you never grow, you never plan for the future. When you chronically turn on the stress-response, your body is forced to ignore the repair and growth functions it would normally be performing, and then you've got this big challenge of how do you recover afterward? This is what chronic stress is about: That same stress-response that was wonderfully adaptive and logical for that zebra or lion, do it chronically, and you pay a price. ■

Important Terms

homeostasis: A state of equilibrium, with physiological endpoints functioning in an optimal range.

stressor: An external perturbation that disrupts homeostasis; also, the psychological anticipation of such a perturbation occurring.

stress-response: The array of hormonal and neural adaptations in the body meant to reestablish homeostasis.

Suggested Reading

McEwen, "Protective and Damaging Effects of Stress Mediators."

Sapolsky, *Why Zebras Don't Get Ulcers*, chap. 1.

Questions to Consider

1. Why is the stress-response exactly what you want to have happening in your body if you're running away from a predator?
2. So why don't zebras get ulcers?

The Nuts and Bolts of the Stress-Response

Lecture 2

When you have a thought, have an emotion, have a memory, things change in your body. Your pancreas releases some hormone you've never even heard of. Your spleen is texting your thymus. Something is happening with blood flow in your big right toe, and what we have is this ... capacity, again as these sophisticated psychosocial humans, to turn on physiology with mere thought.

Let's take a look at the nuts and bolts of the human stress-response. Broadly, there are two systems in the body responsible for it. The first is the nervous system, through which your brain influences events throughout your body; the second is the release of hormonal messengers. How do these two systems work? How are they regulated? And most importantly, what happens with these systems during stress?

The part of the nervous system that handles the stuff you don't have much control over, things that are typically automatic, is called the **autonomic nervous system**. This autonomic nervous system comes in two halves: The first half is the sympathetic nervous system, which controls things like the stress-response. In contrast, the parasympathetic nervous system mediates calm, vegetative functioning. When you eat a big starchy meal or take a nap, you turn on the parasympathetic nervous system. If you get disemboweled by a lion, you turn off the parasympathetic nervous system and turn on the sympathetic. For the most part, they work in opposition, and the stress-response is all about turning on the sympathetic nervous system to an extremely severe extent.

So what regulates the sympathetic nervous system and the broader autonomic nervous system? This is illustrated by a wonderful concept that has run through the field of behavioral biology for some years, known as the triune brain. Obviously, this is not what the brain is really about, but it's a way to conceptualize what's happening, particularly with respect to the autonomic nervous system. The first level of the triune brain is the part of your nervous system that has your hypothalamus and all sorts of brain

stem areas. This part of the brain does regulatory stuff: Your body gets cold, there are sensors that send information up to this part of the brain, and your muscles start shivering. The second layer is the **limbic system**, which is about emotion: lust, rage, petulance, and so on. Sitting on top is the third layer, the **cortex**. The cortex, the most recently evolved part of the nervous system, is about abstract stuff: abstract reasoning, processing, and long-term memories. Think about children in refugee camps, think about your mortality, and you might turn on the stress-response; the nervous system reacts as if this is a physiologically real event.

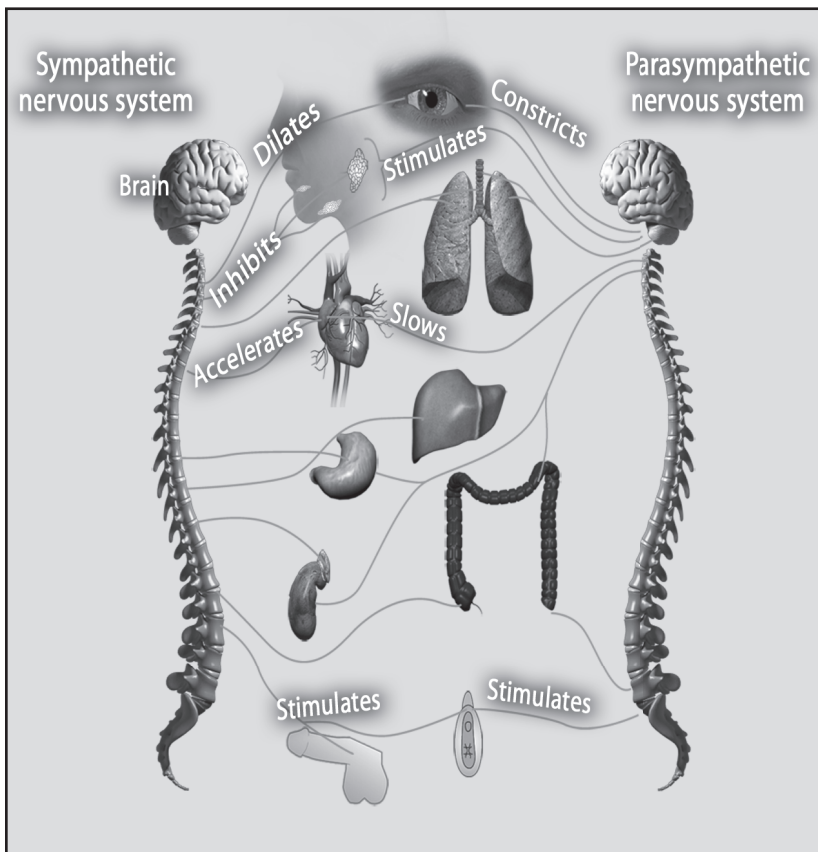


Figure 2.1. The autonomic nervous system.

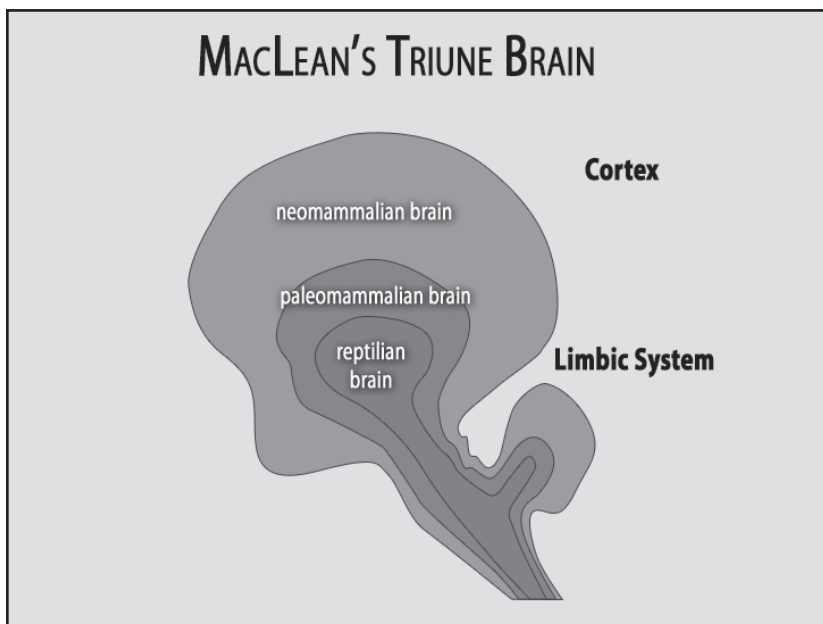


Figure 2.2. The triune brain.

The second type of regulation is by way of hormones. A **hormone** is a chemical messenger from a brain cell or from cells throughout the body; hormones are blood borne and as a result can affect events throughout your body. The brain releases hormones that tell the pituitary gland what hormones to release, which tell the peripheral glands. Which hormones are secreted during the stress-response? After epinephrine, there is a class of steroid hormones that come out of the adrenal glands called glucocorticoids. Stress also increases secretory rates of prolactin, glucagon, and beta-endorphin. Then there are the hormones whose secretion is inhibited during stress, like growth hormone, insulin, and the reproductive hormones.

The interactions of these hormones will be covered in detail in the next few lectures. Note, however, that not everybody has the exact same stress-response. The fact that individuals differ in how their bodies respond to stress is great, because once we figure out the folks who are doing it just right, then we've got a model to go after. ■

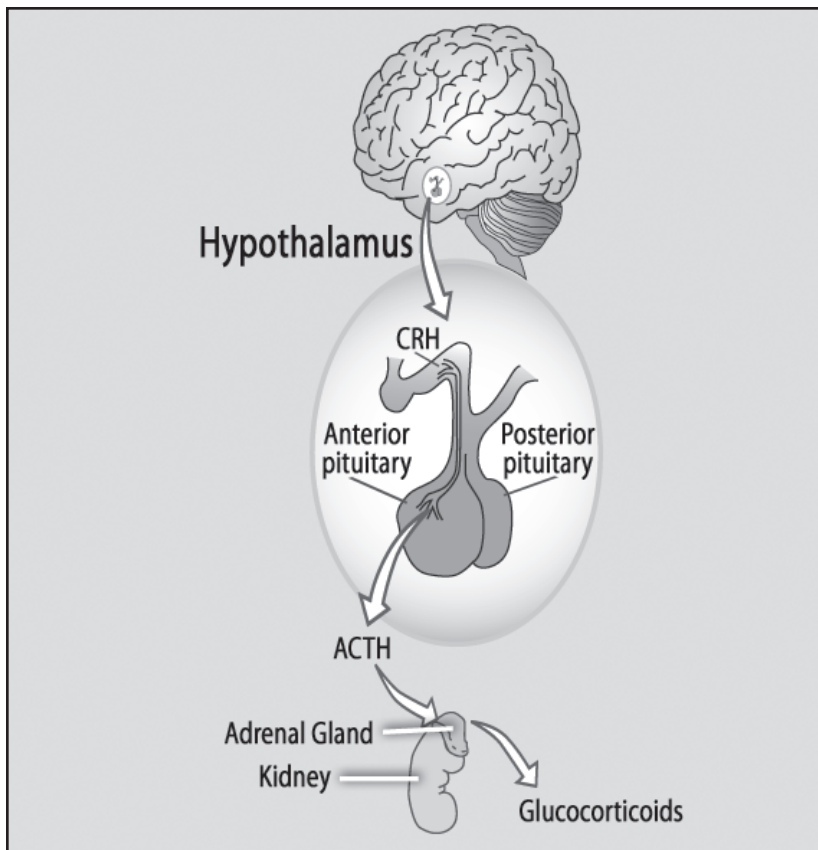


Figure 2.3. The control of glucocorticoid secretion.

Important Terms

autonomic nervous system: A part of the nervous system that mediates aspects of the body's function that are often automatic, or involuntary. Consists of the sympathetic nervous system (generally involved in arousal and stress-responses) and the opposing parasympathetic nervous system (generally involved in calm, vegetative bodily function).

cortex: The outer surface of the brain, it is the most recently evolved and involved in the most abstract brain functions. Most pertinent to this course is the frontal cortex.

hormone: A chemical messenger released by glands into the bloodstream, where it travels and has effects elsewhere in the body.

limbic system: A region of the brain that plays a central role in emotion.

neurotransmitter: A chemical messenger with which one neuron communicates with another. Examples include serotonin, dopamine, and norepinephrine.

Suggested Reading

Sapolsky, *Why Zebras Don't Get Ulcers*, chap. 2.

Questions to Consider

1. How does your brain control hormonal events throughout your body?
2. What are some of the critical hormones secreted during stress, and what do they do?

Stress and Your Heart

Lecture 3

This brings up a point ... that's very well summarized by Elie Wiesel—concentration camp survivor, Nobel Laureate—a phrase that he has often used, which is, the opposite of love is not hate. The opposite of love is indifference. ... Physiologically, quite similarly, ... extreme love, extreme hate, what your sympathetic nervous system can be doing is quite similar.

If you wanted to pick the definitive, iconic outpost of your body that gets done in by chronic stress, the cardiovascular system is the one. There's a lion there, and you have to go running for your life; you had better hope you turn on the cardiovascular stress-response.

It's actually very simple to do: You secrete **glucocorticoids** and **epinephrine**. You turn on the sympathetic nervous system and turn off the parasympathetic. Your heart rate goes up; your blood pressure goes up. The entire process is very adaptive because now you're delivering more blood, more glucose, and more oxygen throughout your body. Because this is a crisis, you're saving your life by sending blood where it's needed, the thigh muscles and the lungs, for example. Meanwhile, you divert blood away from the parts of your body that don't need it, such as your gut and your reproductive organs.

So what happens when you do all of this too long because of chronic stress, especially chronic psychological stress? Increase your blood pressure for 30 seconds and run away from the lion—you're saving your life. Increase your blood pressure chronically, and you are suffering from hypertension.

How does that happen? You have periods of the heart working really hard, pumping with more force, pumping more frequently. Blood pressure is increasing. It's going through the blood vessels with more force, distending the blood vessels out more from the sheer force of it. The blood vessels, in response, slowly begin to build up more muscle wrapping around them. This makes the blood vessels more rigid, which requires more force to

get the blood through there. You increase the blood pressure evermore, and we've got a vicious cycle here. That's how you begin to get problems with hypertension.

What's the price that you pay? Ultimately, the heart is just a big old mechanical pump, and it has a lot of the same principles if you make it work very hard. It

Once the coronary vessels are damaged, when you increase blood flow during a period of stress, they no longer vasodilate; they constrict.

begins to wear out after a while. Enough of that slamming of blood against the walls of the blood vessels and you begin to get little bits of damage there, little bits of tearing and scarring that wind up getting inflamed. You begin to get a bit of a plaque. Now along comes fat and glucose and cholesterol, and that stuff is more likely to stick onto this inflamed little plaque.

That's a problem, but you can set yourself up for a second problem, and this is one that has been shown in a lot of experimental settings. You have hypertension, which could lead to damage to your blood vessels. Very interesting research shows that if you couple hypertension with a high-fat diet, you get far more vascular damage

than either alone. What this brings us to is the third outpost of what can go wrong. It turns out coronary blood vessels, the blood vessels bringing blood to your heart, are not vessels you want to damage from chronic hypertension. Normally there is something really helpful that coronary blood vessels do when they're perfectly healthy. In a crisis, you need more blood delivered to your heart, so a healthy coronary blood vessel will vasodilate: increase, become looser so more blood can go blasting through. But once the coronary vessels are damaged, when you increase blood flow during a period of stress, they no longer vasodilate; they constrict.

You're totally up the creek now. You've got damaged coronary blood vessels, and exactly when your heart needs more energy during a major stressor, these blood vessels stab you in the heart by constricting even more. Your heart, thus, does not get enough blood flow. It doesn't get enough oxygen,

enough glucose, or enough energy, and you have myocardial ischemia. Your heart muscles are not getting enough of the stuff they need. ■

Important Terms

epinephrine: A hormone released during times of stress by the adrenal glands under the control of the sympathetic nervous system; it is also known as adrenaline. Epinephrine plays a key role in virtually all aspects of the stress-response.

glucocorticoid: Any of a class of hormones released from the adrenal gland during stress that play a key role in virtually all facets of the stress-response. The primate/human version is cortisol, also known as hydrocortisone. Synthetic versions often prescribed by physicians include dexamethasone and prednisone.

Suggested Reading

Sapolsky, *Why Zebras Don't Get Ulcers*, chap. 3.

Questions to Consider

1. How is the cardiovascular stress-response perfect for your body while you're escaping a predator?
2. How does chronic stress cause atherosclerosis?

Stress, Metabolism, and Liquidating Your Assets

Lecture 4

Adult-onset diabetes, insulin-resistant diabetes, used to be this incredibly obscure outpost of disease. This was a problem that our great, great, great, great grandparents never thought about. ... It is a disease becoming more prevalent with Westernized lifestyle, putting on weight, becoming sedentary. ... This once obscure disease is slated to become the planet's biggest killer within a couple of decades or so, according to the estimates of the World Health Organization.

Metabolism is the process of how food goes from your gut to beginning to be useful to your body. There are basically 3 constituents in food: protein, carbohydrates, and fat. Your stomach and intestines do their thing, breaking down protein into amino acids, breaking down complex carbohydrates into simple sugars, and breaking down fat into fatty acids and glycerol. You are well fed: You've got, if anything, surplus amounts. What do you do? You store the stuff away in a complex storage form. You do exactly the opposite of the digestion that you have just gone through.

How do you do that? The pivotal hormone that's involved is **insulin**. You secrete insulin in response to elevated nutrient levels in your bloodstream, or even in anticipation of a meal. Along comes an acute stressor. You need energy not stored away but powering whichever muscles are going to save your life. You break down the storage forms of energy and flush them into the circulation. And you do something else: You secrete glucocorticoids,



A glucometer measures the concentration of glucose in the blood.

© Creas/Thinkstock

glucagon, and epinephrine. You mobilize stored energy forms, and you shut down insulin secretion so that you're not storing anything. This is not a good thing. Your metabolism normally allows you to store energy for the future. But when you enter a cycle of chronic stress, you mobilize energy, store it away, then mobilize it again. Our biochemistry of storage and mobilization is not 100% efficient; it costs a little bit to break them down and mobilize them again and again.

Metabolic syndrome encompasses an array of symptoms that increase your risk of metabolic disease and/or cardiovascular disease.

Another potential problem is **diabetes**. If you've got juvenile (Type 1) diabetes and are chronically stressed, this starts a vicious cycle. Each time you get stressed, you're releasing a flood of sugar into your bloodstream and then storing it away. You are doing the very opposite of what blood sugar control is about in diabetes: You're getting huge oscillations all over the place. Chronic stress makes glycemic control (control of sugar) more precarious for a person with diabetes. Type 2, or adult-onset, diabetes is coming to haunt modern Western societies. The problem here isn't too

little insulin; it's an excess of nutrients. Typically, you are getting older in a Westernized way: You put on weight, you become more sedentary, and you've got all these excess nutrients in your bloodstream. What's the logical thing you would be doing at this point? Store away the excess. But your problem is you've stored so much away already that your fat cells are full. One additional step occurs: Your brain indirectly sends a signal to fat cell storage sites throughout your body and says, "Don't listen to any insulin. Become resistant to it; lose your sensitivity to it."

This insulin resistance can lead to hyperglycemia, which can lead to cardiovascular damage and increase your risk of metabolic disease. Suddenly, they are completely intertwined, which is the rationale behind the large catchment term for what can go wrong in this realm, **metabolic syndrome**. Metabolic syndrome encompasses an array of symptoms that increase your risk of metabolic disease and/or cardiovascular disease. It illustrates the concept that you can't put parts of your body into completely

separate categories; you solve local challenges to homeostatic balance with adaptations far flung throughout your body. ■

Important Terms

diabetes: Type 1 (juvenile) diabetes is an autoimmune disorder in which the pancreas is unable to secrete insulin. Type 2 (adult-onset; a.k.a. insulin-resistant) diabetes is a disorder, typically brought on by obesity, in which cells throughout the body have become resistant to the effects of insulin.

glucagon: A hormone released from the pancreas during stress that helps mobilize energy from storage sites in the body.

insulin: A hormone released from the pancreas that promotes the storage of glucose throughout the body. It is normally secreted when blood glucose levels rise; secretion is inhibited in the early phases of the stress-response.

metabolic syndrome: An emerging concept in medicine focusing on the fact that there is often overlap between the causes and symptoms of cardiovascular disease and of metabolic diseases such as diabetes; the syndrome refers to a constellation of symptoms that can include hypertension, obesity, hyperglycemia, and insulin resistance.

Suggested Reading

Rubin, *Diabetes for Dummies*.

Sapolsky, *Why Zebras Don't Get Ulcers*, chap. 4.

Questions to Consider

1. What do you normally do with excess energy in your circulation?
2. How does stress push you into adult-onset diabetes if you are just on the edge of having the disease?

Stress, Overeating, and Your Digestive Tract

Lecture 5

Let's now think about chronic stress. You've got someone who says, "Oh my God, I'm so stressed. I get stuck in traffic every day, I have a horrible boss, my relationship is unsteady, all of these sorts of things, and I am like totally stressed nonstop, 24-7." This is not like totally stressed nonstop 24-7. You want to know what totally stressed 24-7 is about, you look at somebody with a whole body burn, and you look at somebody in septic shock. That's stress 24-7. ... What we call everyday chronic stress is instead lots and lots of intermittent stressors.

Let's look at the gastrointestinal tract. Once the food gets into your mouth and then your esophagus, your stomach, and your intestines, what role does stress play? Of course the first issue is how desirous you are of putting food in your mouth. What does stress do to appetite? About two-thirds of people eat more than usual when they're stressed. Why? A piece of what's occurring is psychological. It turns out those two-thirds of people have something in common, which is on a regular basis, when they are eating a meal, they are consciously regulating the amount of food they take in. Along comes stress, and what happens is you say, this is an incredibly stressful period, enough of that self-regulation; I am going to gorge. What you do during stress is you tend to suspend some of the regulatory processes, some of that self-discipline.



©Michael Blann/Digital Vision/Thinkstock

Work-related stressors are among the causes of gastrointestinal disorders.

There's an additional reason why most people wind up eating more food when they're under stress. Your brain, with the onset of stress, secretes a particular hypothalamic hormone that causes the pituitary to secrete a hormone that stimulates the adrenals to release glucocorticoids.

Alongside the insulin effect we learned about in Lecture 4, something else happens. The glucocorticoids stimulate appetite so that you replace all the energy you depleted running for your life. At the end of stress, it takes quite a few minutes for glucocorticoid levels to go back to normal. In other words, after any given stressor, there's a period of increased appetite.

There is a great dichotomy between 2 different types of fat: abdominal fat and gluteal fat.

Let's now think about chronic stress. If you spend all day having bursts of intermittent stressors, you are spending a lot of the day recovering from them. Your appetite increases, and generally you crave carbohydrates: bread, sugars, treats, and candy. For even more bad news, we now consider

where those excess calories go. They go into your fat cells, but all fat cells are not the same. There is a great dichotomy between 2 different types of fat: **abdominal fat** and **gluteal fat**. Abdominal fat is more dangerous, for a whole bunch of reasons. It releases inflammatory signals, which can be a greater risk in your torso than in other parts of your body; it sits close to your liver, which could lead to fatty liver; and its sheer mechanical pressure pulls your spine forward. Abdominal fat puts more stress on your body.

What happens to your gastrointestinal tract under chronic stress? All sorts of things can go wrong: You turn off the digestive tract, and if you do this chronically, disease risk is going to crop up. Gastrointestinal disorders are a bit confusing, but they basically come in 2 flavors: organic bowel disorders and functional bowel disorders. Organic bowel disorders are those that have an explanation, such as an abnormality in the structure of your small intestines or lactase not performing correctly. Functional bowel disorders are what they diagnose you with when they haven't a clue what's up. But we do know that functional bowel disorders are exquisitely sensitive to stress. This is the realm of things like irritable bowel syndrome and spastic colon. This is

the realm in which emotions, by way of the autonomic nervous system and stress hormones, can greatly regulate your bowels.

This reemphasizes the central concept of the overlap between the organic and psychogenic bases of disease. If all you do is concentrate on 1 piece of the story, you're not going to know what's going on. It's the intersection that is critical and informative. ■

Important Terms

abdominal fat: Fat deposits around the gut. Chronic stress preferentially promotes the deposition of abdominal fat, which is of the type that is worse for cardiovascular health.

gluteal fat: Fat deposits around the buttocks.

Helicobacter pylori: A bacteria that causes a large percentage of cases of peptic ulcer. Chronic stress can impair the ability of the body to repair such ulcers.

ulcer: An area of tissue erosion (e.g., on skin or on the stomach lining).

Suggested Reading

Adam and Epel, "Stress, Eating and the Reward System."

Sapolsky, *Why Zebras Don't Get Ulcers*, chap. 5.

Questions to Consider

1. What does stress have to do with craving carbohydrates?
2. Despite the discovery of a flashy bacteria that causes ulcers, why does stress help explain why only some people infected with the bacteria develop an ulcer?

Stress and Growth—Echoes from the Womb

Lecture 6

Take a newborn rat, and over the first couple of weeks of its life, pick it up every day and handle it. Pet it for a few minutes. ... What this counts as is stimulation, and remarkably this is now a rat who, as an adult, will have lower glucocorticoid levels, that will have better learning and memory, and as it turns out will have a more neurologically intact old age.

What does stress have to do with child development? The critical fact is that environment doesn't begin at birth. Environment begins in fetal life, and thus the consequences of stress can begin in fetal life also. What's environment like for a fetus? What it's about is what mom is experiencing, because you share her circulatory system, and the hormones in her bloodstream will wind up, to some extent, in your own circulatory system. The amount of nutrients is relevant, as are things like extremely loud noises.

You don't want to be a stressed fetus. There are 2 realms of consequences of fetal stress. The first is what you're like at birth; at the simplest level, more fetal stress equals a lower body weight at birth. The other, more subtle, point is that fetal experience influences what sort of adult body you're going to have as you respond to adult environments. Things get regulated in a permanent sort of way during fetal life. This phenomenon has been termed **fetal origins of adult disease**, a completely new area of research built around the notion that environment doesn't begin at birth. An awful lot of what's going on in fetal life causes programming of how adult responses are going to be.

It's the same outcome in a child as opposed to a fetus. Chronic activation of the stress-response does all sorts of bad stuff. If you stress an infant rat, you produce an adult rat with higher glucocorticoid levels and who has trouble turning off glucocorticoid secretion at the end of stress. Your rat will have a somewhat activated stress-response all the time and be more vulnerable to relevant diseases. Your rat will be not as good at learning and memory and will be more prone toward anxiety. Chronic stress leads to all sorts of long-term consequences.

The other component that comes into the equation is mothering style. Different styles of mothering can represent and generate a more stimulatory environment, or a less or more stressful one. Studies on rats and primates have shown that mothering style translates into different adult stress-responses in the offspring. So experience, prenatal and postnatal, can shape the sort of hormonal profile and brain you have as an adult. Early experience—taking the form of severe stress, but also mild stress, degrees of stimulation, and mothering style—produces different profiles in adulthood, and even in following generations.



© iStockphoto/Thinkstock

Prenatal and childhood stress lead to a variety of negative health outcomes in adulthood.

If you are stressed prenatally for 3 minutes, are you going to pay a price? No, there are enormous amounts of variability from one individual to another. Developmental stress does not guarantee that you will suffer those effects. The other piece of good news is that the negative effects are not necessarily permanent: There's a tremendous capacity to reverse them throughout life. ■

Important Terms

benzodiazepines: Anxiety-reducing tranquilizers such as Valium and Librium. The brain contains receptors for them, indicating that the brain makes still-undiscovered natural versions of these drugs.

fetal origins of adult disease (FOAD): This is an emerging concept in medicine, focusing on the fact that events during fetal life can program lifelong aspects of bodily function. As the example covered most in this course, fetal malnutrition often causes increased insulin secretion throughout life.

The Dutch Hunger Winter Phenomenon

In 1944, Holland was occupied by the Nazis. For a number of reasons, including the uprising of resistance among the Dutch against the Nazis, the decision was made to punish Holland and divert all of the food that winter to Germany. Holland, with its reasonably good Westernized diet, suddenly plunged into famine. Something very interesting came out of this.

Suppose you are a second- or third-trimester fetus during the Dutch Hunger Winter. You are experiencing starvation, as there are fewer nutrients in mom's bloodstream. Your body concludes that there's not a whole lot of food out there in the world. Thus, your body gets programmed to be thrifty. Every bit of food that hits your bloodstream, quick, store it away, secrete insulin like crazy. Every bit of salt that you have, your kidneys are really good at retaining it because who knows when the next salt is coming.

The Dutch Hunger Winter ends, and you're back to a normal, healthy Dutch diet. Everything else being equal, 50 years later, you will be about 20 times more likely to have metabolic syndrome, because your body learned as a fetus to be really thrifty at storing away nutrients, and you have programmed your metabolic system to work that way forever. This is one of a number of examples of a new area of research called fetal origins of adult disease.

There's an even more interesting ripple to this, which is it turns out that Dutch Hunger Winter effects are multigenerational. If you were a Dutch Hunger Winter fetus, and 30 years later you are pregnant, your thrifty metabolism will impact your fetus. You have a perfectly typical diet during your pregnancy, but you are more efficient at taking nutrients out of the bloodstream, so your fetus is getting fewer nutrients than it should. In other words, Dutch Hunger Winter babies generate Dutch Hunger Winter babies, and their grandchildren show some of these same tendencies.

Suggested Reading

Godfrey and Barker, “Fetal Programming and Adult Health.”

Sapolsky, *Why Zebras Don't Get Ulcers*, chap. 6.

Questions to Consider

1. How is it that environment doesn't begin at birth?
2. Why does being starved as a fetus make you more likely to have diabetes at age 60?

Stress, Growth, and Child Development

Lecture 7

The general consensus in the field is [stress dwarfism] is a remarkably rare disease. This is a once-in-a-career disease to see, extremely rare. Except, it's not so rare. It pops up all over the place. It pops up in areas of—perfectly logically—extreme stress, for example ... these poor kids who were raised in the Romanian orphanages shortly after the fall of Communism there.

If you are a young person and are chronically stressed, you're not going to grow as fast. What are some of the mechanisms underlying this? Some very straightforward ones like elevated levels of glucocorticoids, elevated activation of the sympathetic nervous system, and decreased secretion of growth hormone. The cardiovascular stress-response also plays a role: Your blood pressure goes up to deliver energy to the thigh muscles, but you decrease blood delivery to unessential areas like your gut. If you are a kid and are chronically decreasing blood flow to your gut, you're not absorbing nutrients as readily.

The effects of stress on child development are not subtle, and at an extreme, you get one of the truly bizarre, disturbing outposts of medicine: **stress dwarfism**, a disease of kids who are so stressed that they stop growing entirely. These are children who have no obvious disease. There is no malnutrition. There are no parasites. You look in the bloodstream, and there's no growth hormone. You give them synthetic growth hormone. Nothing happens; the whole system is shut down. What you have here are the consequences of truly sustained stress. You check around with that kid's background, and out comes some appalling psychological stressor. The good news is the consequence of removing that child from that stressful setting: Get them into a different setting, and everything gets better. There is a profound capacity of stress to disrupt growth but also a remarkable capacity of children to recover from it.

A remarkable therapy was worked out a few decades ago by a psychologist at the University of Miami named Tiffany Field. She noticed that one of

the triumphs of modern medicine had a major downside: Kids in neonatal intensive care units are taken care of with all sorts of sophisticated equipment, but in the process, they don't have a lot of physical contact with people. Field came up with the idea of physically stimulating severe preemies, going in and massaging their backs 3 times a day. She discovered something remarkable, which was about a 50% increase in the growth rate in the preemies who were stimulated in this way. The babies were more alert, they were more active, they went home at an earlier stage—and looking at them months later, their growth rates were still enhanced.

We know you secrete less growth hormone during stress. But what does growth hormone do? In kids, it makes you grow. And it turns out that in adults, it helps remodel your bones. Growth hormone plays a huge role in depositing new calcium into bones. Along comes chronic stress, growth hormone levels drop, and you are now depositing less calcium into your bones. What's that going to set you up for? Brittle, prematurely aged bones and osteoporosis. The moral of the story is chronic stress at any age is not a good thing. ■

King Frederick II, Early Endocrinologist?

King Frederick II of Sicily, a 13th-century despot, carried out a remarkable experiment. The members of his court were having an argument about what the natural language of humans is. One thought it was Greek, another Latin or classical Hebrew, and Frederick II was holding out for Italian. So what did he do? He commandeered some children in his kingdom and had them raised in complete isolation for a number of years—no one talking to them, just someone silently running in and leaving food for them; minimal contact with other humans. The notion in this experiment was that at some point they would open the door and the children would come out reciting in classical Greek or whatever the natural language of humans was. Eventually they opened the door, and the kids did not come out speaking classical Greek; the kids did not come out at all. They had died from the extreme of stress dwarfism.

Important Term

stress dwarfism (a.k.a. **psychogenic dwarfism**, **psychosocial dwarfism**): A disorder in which growth in a child is significantly impaired by severe psychological stress.

Suggested Reading

Sapolsky, *Why Zebras Don't Get Ulcers*, chap. 6.

Questions to Consider

1. Is stress dwarfism as rare as most clinicians think?
2. What are the effects of stress early in life on the developing brain?

Stress and Female Reproduction

Lecture 8

[In] a study of gymnasts ... from the Romanian Olympic gymnastics team—and those are typically those 15-year-olds who weigh 60 pounds and are getting the gold medals—what was the average age at which these kids started menstruating? It was approximately 19. The Western average is 12 1/2 years; this is a huge effect in terms of delaying the onset of puberty.

Female reproduction falls under the auspices of those big, long-term, optimistic projects that the body neglects when faced with chronic stress. A great way to appreciate just how much this is one of those indulgences is to look at how expensive some aspects of female reproduction are. The best estimates are that you spend 50,000 calories over the course of a pregnancy and about 1000 calories a day nursing. This is something that's tough to afford when you're running for your life.

What are the hormones involved? At the follicular stage, it's that same axis we've discussed before: brain, pituitary, and peripheral glands. The brain's hypothalamus releases the **luteinizing hormone**, telling your body to prepare for fertilization. Meanwhile, you are releasing **follicle-stimulating hormone** out of your pituitary. These 2 hormones mature eggs and produce estrogen. Once you transition to the luteal phase, progesterone dominates. This hormone prepares the uterus, thickening it for implantation of the fertilized egg.



Exercise has wonderful stress-reducing effects, but overexercise can decrease fertility.

© Brand X Pictures/Jupiterimages/Thinkstock

So what happens during stress? There is decreased brain release of the luteinizing hormone, which in turn tells the pituitary to release less luteinizing hormone and follicle-stimulating hormone. The decreased amount of these hormones makes the ovaries less stimulated to release estrogen. The result is lower estrogen levels and less likelihood of fertilizing an egg. Moreover, stress hormones like glucocorticoids and **beta-endorphin** are also blocking the release of progesterone. Your body doesn't thicken the uterine walls, and it's less likely that the rare fertilized egg is going to implant there.

What other aspects of female reproduction are negatively impacted by chronic stress? Starvation, including the voluntary starvation of anorexia nervosa, can shut down ovulation. This is due to the depletion of fat. That's also the reason why some women who do tons of exercise stop ovulating. For example, runners who run about 50 miles a week begin to see their fat deposits dip below a threshold where they begin to have ovulatory problems.

Another domain where stress becomes relevant is high-tech reproduction, in vitro fertilization. This process is enormously stressful: Your lifestyle is dislocated, you are filled up with synthetic hormones that wreak havoc with mood and metabolism, and sex becomes a timed chore.

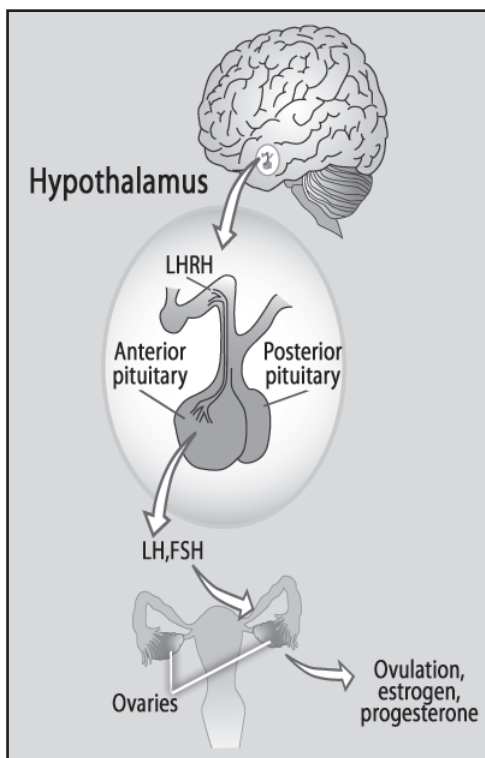


Figure 8.1. Female reproductive endocrinology.

You spend a fortune on it, usually not reimbursed by insurance, and there is a very high failure rate. There hasn't been clear-cut evidence for this yet, but it seems an obvious conclusion that stress makes in vitro fertilization less likely to work.

Another possibility in terms of stress and reproduction is you've gotten a pregnancy to start and chronic stress causes a miscarriage. This is not caused by a horribly stressful event you had one day; this is from stressors stretching out quite a few days. Women who are chronically severely stressed when they're pregnant decrease blood flow to the fetus; if that happens enough, it increases the likelihood of losing the pregnancy.

Lastly, chronic stress decreases your libido. The parts of your body that are sensitive to tactile stimulation are more sensitive when you have high levels of certain reproduction-related hormones in your bloodstream. Those hormones decrease, and sensitivity in those areas is blunted. One additional piece is a brain chemical called dopamine, which has everything to do with pleasure. Sex tends to release dopamine. With chronic stress, you don't have as much dopamine in the pathway, and suddenly sex is less pleasurable. ■

Important Terms

beta-endorphin: A hormone released during stress, predominately from the pituitary gland. It plays a role in stress-induced analgesia and in some of the disruptive effects on reproduction.

follicle-stimulating hormone (FSH): A pituitary hormone that stimulates follicle maturation in females and sperm maturation in males.

luteinizing hormone (LH): A pituitary hormone that stimulates estrogen synthesis in females and testosterone synthesis in males.

prolactin: A hormone released from the pituitary gland in response to stress, exercise, and nursing. It inhibits aspects of reproductive physiology.

Suggested Reading

Sapolsky, *Why Zebras Don't Get Ulcers*, chap. 7.

Tilbrook, Turner, and Clarke, "Effects of Stress on Reproduction in Non-Rodent Mammals."

Questions to Consider

1. What is a consequence for women of excessive amounts of exercise?
2. What, if any, is the link between stress and miscarriage?

Stress and Male Reproduction

Lecture 9

Apparently it's not fun to be in the Marines. Apparently, it's kind of a drag, in fact, especially during military training. This was this classic study, 1970, *New England Journal of Medicine* looking at military officers' training during this first couple of months. In addition to all the other indignities, these guys had to pee into these little Dixie cups where ... the endocrine people would analyze their hormone levels. Back comes the finding that you look at guys during the first couple of months in the Marines, and they've got the circulating testosterone levels of newborn babies.

Let's switch over to making sense of the male reproductive system and the effects of stress. Short-term, if you're running for your life, it makes sense for your body to decide to make sperm some other time. But do it chronically, and you are going to pay a price. It all revolves around testosterone, this key steroidal hormone that comes out of the testes. The endocrine axis for testosterone goes from the hypothalamus to the pituitary to the testes. This system in males is actually a lot simpler than in females. The female reproductive axis has to have cyclic release, and that takes some very fancy wiring. The male brain, in contrast, just needs to release a certain amount of testosterone on a regular basis.

It turns out the problem during stress is not that testosterone levels go down; the problem is erectile dysfunction.

Nonetheless, amid that simplicity, the male reproductive system is vulnerable to stress in some of the same exact ways. With the onset

of stress, testosterone levels go down. Weirdly, it's almost the exact same hormones involved as those in women. From the pituitary, out come follicle-stimulating hormone and luteinizing hormone, which stimulate, respectively, the production of sperm and testosterone. Numerous studies have shown these decreases in testosterone levels in men in circumstances ranging from undergoing surgery to taking final exams to beginning military training.

What are the physiological consequences of testosterone levels going down during stress? There actually is a very surprising finding, which is there are no consequences of testosterone levels going down during stress. Testosterone turns out to be a vastly overrated hormone. It's virtually superfluous. You've got to knock down levels of it enormously in order to impair fertility. It turns out the problem during stress is not that testosterone levels go down; the problem is erectile dysfunction.

What happens during stress? In scenario 1, you can't turn on the parasympathetic nervous system, so you have the problem of stress-induced impotency. In scenario 2, you get anxious and accelerate the transition from the parasympathetic to the sympathetic nervous system, leading to premature ejaculation. This is a world of extraordinary vulnerability, erectile dysfunction. Either you can't get the erection, or you have premature ejaculation. It is incredibly easy for this to occur.

Current estimates are that 60% of the doctors' visits in this country are due not to organic cases of impotency but to psychogenic, stress-related cases. This is a system that is spectacularly vulnerable to stress effects. In circumstance after circumstance, what we see is stress of all sorts, physical or psychogenic, shutting down the reproductive system. ■

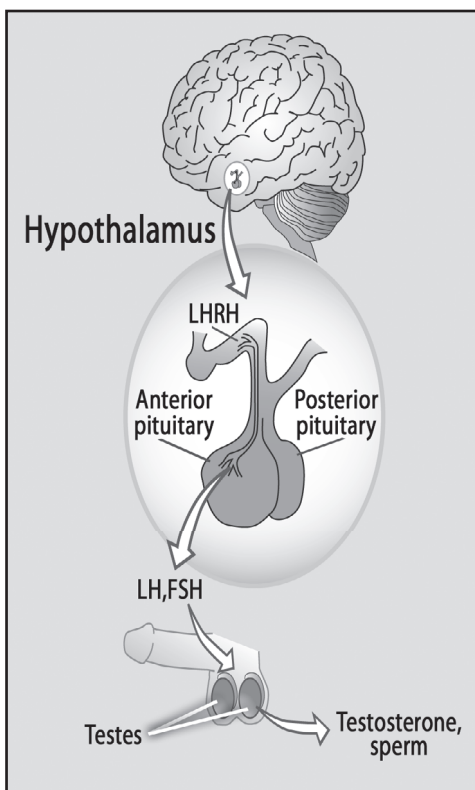


Figure 9.1. Male reproductive endocrinology.

Suggested Reading

Sapolsky, *Why Zebras Don't Get Ulcers*, chap. 7.

Questions to Consider

1. What are the effects of stress on testosterone levels, and what are the consequences?
2. What are the effects of stress on erections?

Stress and Your Immune System

Lecture 10

The evidence that something as bizarre as what's happening in your head can influence your immune system ... in fact goes back quite a few centuries. The first evidence for this was this wonderful study back in the 1800s, and I wish I knew who had the intuition to do this; but you take people back when, with a rose allergy, and you get ... an artificial rose ... and you wave it in front of one of these people's noses. They suddenly start sneezing, not because this was a real rose, but because of psychoneuroimmunology kicking in. Their immune system, their inflammatory system in this case, got tricked into starting to sneeze.

While back, words like “endocrinology” or “neurobiology” were satisfyingly long. In recent years, though, we have even longer terms: psychoendocrinology, behavioral socioendocrinology, neuroeconomics, and even neuromarketing. There is another multisyllabic term, with some of the most syllables around: a brand new field called psychoneuroimmunology. This field examines what's going on in your head and how it impacts your immune system.

How does the immune system work, and how is it affected by stress? The immune system is unbelievably complicated, but in a nutshell, it protects you from pathogens—invasive things that don't belong in your body and could make you sick (most broadly, bacteria and viruses). This is done in wildly complicated ways. For one thing, all sorts of subtypes of immune cells activate the system, suppress the system, activate the suppressors, and suppress the activators. New immune cells are made in various places: in your bone marrow, in your thymus gland, in your spleen, and in your lymph nodes. Broadly, there are 2 categories of immune cells, or lymphocytes: T cells and B cells. T cells originate in the thymus; B cells originate and mature in the bone marrow. That's a very simplified version here for our purposes.

T cells and B cells do very different things. B cells are constantly surveying your body to look for pathogens. When they encounter a pathogen, they

have the brilliant capacity to recognize that it doesn't belong there, and they start to make antibodies specific to this pathogen. Naturally, pathogens aren't just sitting there passively getting blown over by the immune system, and just as the immune system has evolved to be fancier, pathogens have evolved to have fancier defenses. T cells and B cells are the 2 basic features

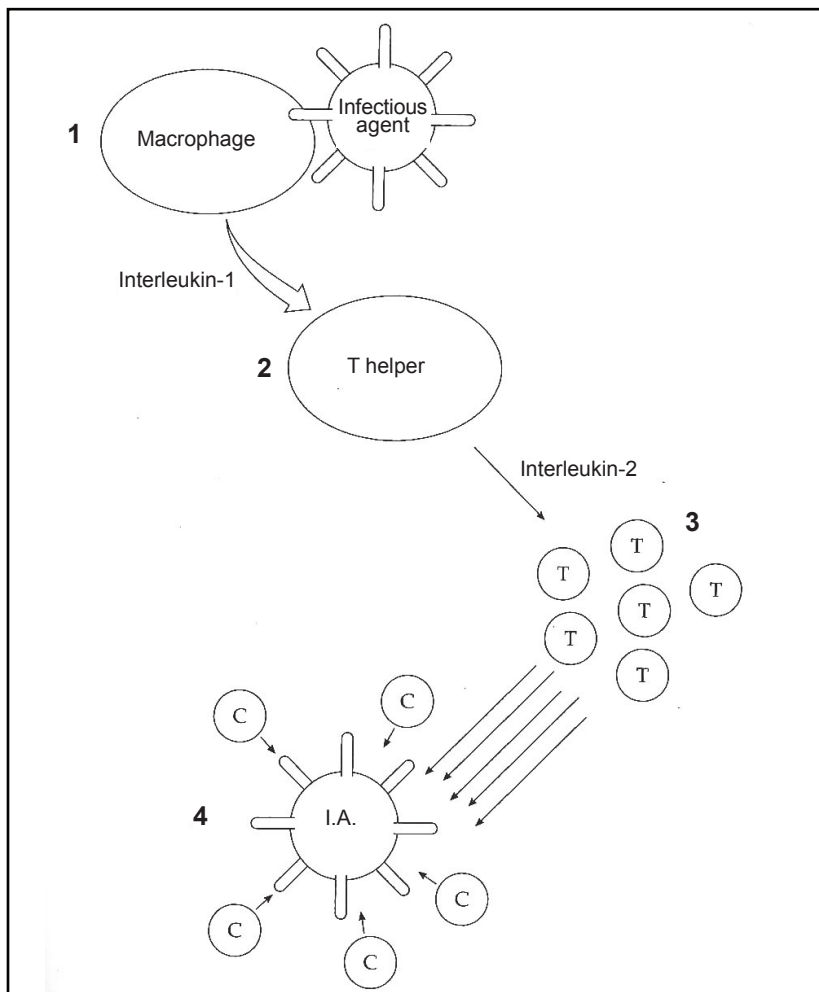


Figure 10.1. Cell-mediated immunity.

of the adaptive immune system, the fancy stuff. Then there is this ancient part of the immune system called innate immunity. Innate immunity is all about inflammation. It just kicks in with any sort of infection, any sort of injury. You get a cut, and you have inflammation there, set to attack any bugs that get in through your injury.

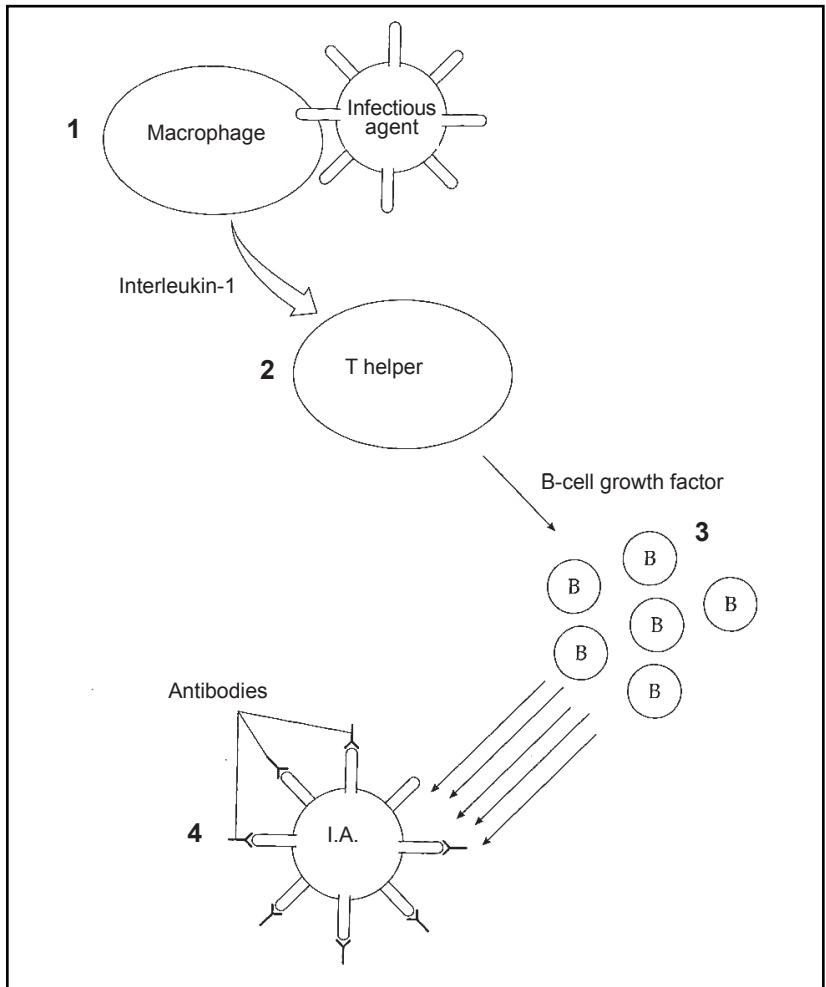


Figure 10.2. Antibody-mediated immunity.

What can go wrong when stress is introduced? The first thing that happens has to do with that short-term stress-response and its short-term effects on immunity. You begin to see an increased risk of autoimmune diseases. These are diseases that cause your immune system to decide that a part of you that is normal and should be there is, in fact, some invasive pathogen. There's a whole array of autoimmune diseases. We've begun to see a hint in the literature that with the onset of lots of stressors, where you activate the immune system over and over, you increase the likelihood of the immune system overactivating into autoimmunity. So we see a relationship between chronic stress and flare-ups of autoimmune diseases. What you see with excessive stress is something very different. Not only with each stressor do glucocorticoids get secreted and bring the immune system back to baseline, but with enough stress, you have the immune system not only going back to baseline but being suppressed below where it normally is, leading to the grave phenomenon of immunosuppression. ■

Suggested Reading

Sapolsky, *Why Zebras Don't Get Ulcers*, chap. 8.

Sternberg, *The Balance Within*.

Questions to Consider

1. Why does chronic stress suppress immunity?
2. What is the link between stress and the likelihood of getting certain infectious diseases?

Stress and Cancer

Lecture 11

In people with AIDS, one of the things you see is an increased risk of certain types of cancers, one called Kaposi's sarcoma. Severe immune suppression increases the risk of cancer. All things considered is the fact that the immune system is just ground down to nothing in HIV, and only a relatively small subset of AIDS patients come down with this cancer. Making that same point again, you've got to absolutely push the immune system down to the floor, and on the simplest level, stressors just don't do that.

The most challenging topic in this whole field is what does stress have to do with cancer? Cancer is a problem of uncontrolled growth: cells that are growing much faster than they should. During fetal and childhood development, your body is all about things growing, and when a particular type of growth has gotten to where it's supposed to be, the relevant genes switch off and ideally are switched off for the rest of time. Cancer is an accidental reactivation of those growth genes, called oncogenes.

So what is the relation between stress and cancer? Everybody knows that stress causes cancer, or at least increases the risk of getting cancer. And once you have cancer, stress makes tumors grow faster and makes relapse more likely. This is one of the most commonly held beliefs about how cancer biology works and how stress-related disease works. Not so fast—it is time for us to start dissecting this belief.

First let's look at the laboratory. What is found there? Lots of stress and lots of glucocorticoids increase the risk of cancer in laboratory animals. And once they have cancer, stress accelerates the progression of the tumor. But how does this translate to humans? Right off the bat, we have lots of reasons to pay no attention to those laboratory studies. Because scientists can't sit around and wait for 10% of their rats to come down with spontaneous cancer, they inject cancerous cells into the lab rat to see whether they take off as a tumor. Because human cancers are not due to being injected with

tumorous cells, there's the disturbing issue of whether lab rat studies are in fact pertinent to human cancer.

This is a particularly tough field because lots of folks go into it with the belief that there is a causal relationship between stress and cancer. It has taken some enormously obsessive, aggressively detail-oriented research to try to pick apart this issue in humans. What do we know in humans about stress increasing the incidence of cancer? At first glance, this appears pretty straightforward: Studies show that people with a stress history have a higher likelihood of coming down with cancer. But there's a problem with a

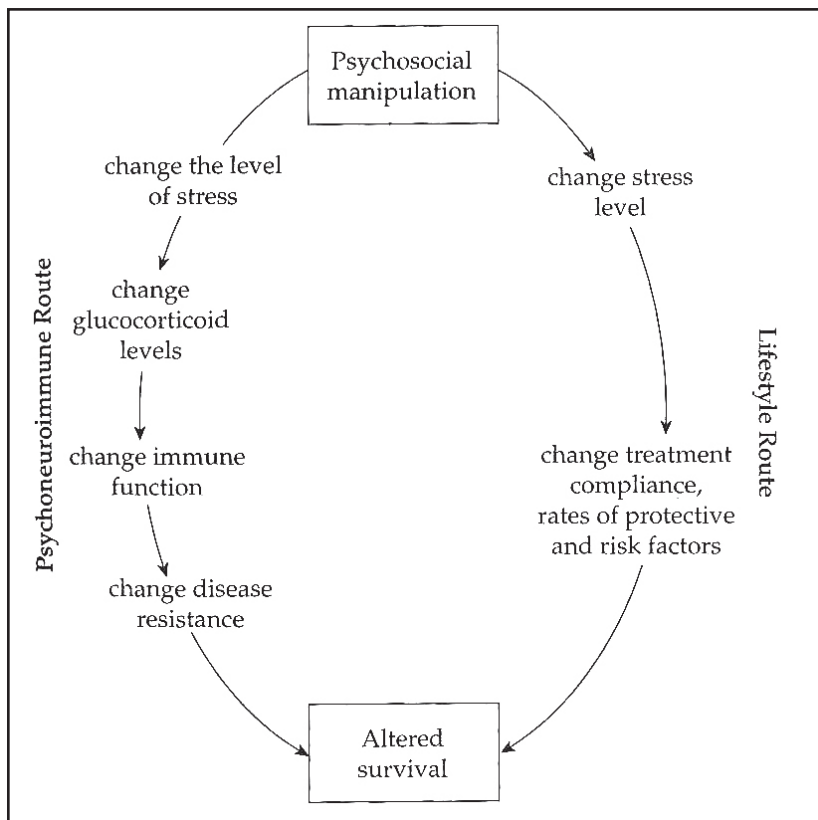


Figure 11.1. The link between chronic stress and disease risk.

number of these studies, which is that they are retrospective. In other words, somebody comes down with cancer, and you then find out what stressors they had in their life, sometimes by asking them. This problem is that

What seemed to be one of the strongest links between stress and cancer is instead probably a compliance issue.

when something bad is going on, our memory is preferentially focused on bad things. When someone has a cancer diagnosis and you ask them about stress in their life in recent years, they tend to remember the bad stuff. When you control for stress, cancer patients have a higher rate of remembering stressors than noncancer patients, as do patients with severe cancer over people with less severe cancer. Retrospective data are very shaky for those reasons. Prospective studies, on the other hand, are considered the gold standard. These involve following a healthy population of people over the years and seeing

if they come down with cancer. A number of these studies have suggested that lots of stressors in life increase the risk of cancer, but even these studies often have confounds, making them hard to evaluate.

How about a next realm of stress—the notion that certain personalities increase the risk of cancer? This has been a wildly controversial field. In general, the literature showing on this has been pretty unimpressive. How about the next step in the progression? You’ve had a successful treatment, and your cancer has gone into remission. Does stress have anything to do with the likelihood of a relapse? There is minimal evidence on this at best. What about the rate of progression, the rate at which the cancer grows? This one is controversial as well. Roughly half of the studies support the idea that supportive group therapy and other psychotherapeutic interventions slow cancer progression, but about half do not. What might actually be going on? In the context of supportive therapy, patients tend to support each other’s compliance with treatment plans. What seemed to be one of the strongest links between stress and cancer is instead probably a compliance issue.

Why is this such an important topic? Because there are highly credentialed charlatans out there who take advantage of it. These are often very influential and credentialed medical experts, pushing their brand of stress management

to slow down or reverse your cancer. But the science simply isn't there. If you push the view that there is a causal relationship, that is bad science, bad medicine, and ultimately bad ethics. ■

Suggested Reading

Cohen, Janicki-Deverts, and Miller, "Psychological Stress and Disease."

Sapolsky, *Why Zebras Don't Get Ulcers*, chap. 8.

Questions to Consider

1. What is the evidence that stress can directly increase the likelihood of cancer occurring and of it progressing more quickly?
2. How might stress play a very indirect route in cancer progression?

Stress and Pain

Lecture 12

You're eating wildly spicy food to the point where it hurts. You've got sweat running down your nose, and you're taking great pleasure in this. ... People long wondered why spicy food at an extreme can hurt, why spicy food tastes hot. Remarkably, it turns out that this capsaicin, this chemical found in hot peppers, actually activates some of those hot receptor neurons. Spicy food that is hot is literally activating the hot pain system.

Pain is utterly intertwined with stress: Pain constitutes a stressor, and stress can cause you to change your sensitivity to pain. In other topics in this course, the pattern has been that in the short term, stress-response is good, but in the long term, it is bad. The biology of pain is the one exception to this rule. Pain is wonderful when it comes at the right time, allowing you to change your behavior and decrease the source of damage. But when there's nothing you can do, pain can be a misery.

Pain starts off with sensors all over your body that pick up when something is going wrong. These are on the level of your skin, your muscles, your organs, and so on. These sensors respond to pain signals by sending that information to your spinal cord and up to your brain. You have pain sensors, for example, that are sensitive to heat, to cold, to pressure, and to when you've cut your skin.

How is the pain signal processed in your spinal cord and up to your brain? The Wall-Melzack model (see below) is the dominant model in the field and gives wonderful insight as to how this system works. It is highly schematic; your neurons don't actually look like this. In part A, we have a neuron in the middle, marked X, that sends a projection to the brain. This neuron is sitting in your spinal cord, and when it is stimulated, it sends a signal telling your brain that something painful is happening. The projections above and below neuron X are coming from pain sentinels somewhere to the left of the diagram. There are 2 types of pathways that could stimulate neuron X, those for sudden pain and those for slow pain.

Part B shows a bit more detail. There is a second neuron, neuron Y, in your spinal cord. Neuron Y sends a projection to neuron X, making it less excitable. So, for instance, your sudden-pain receptors respond to your getting a cut. They send that signal to neuron X and stimulate it, and you feel pain. At the same time, that same sudden-pain neuron has a cable that sends a projection to neuron Y and stimulates it. So with a slight delay, neuron Y turns off neuron X. This is why you get a sharp pain that subsides shortly afterward. When it is the slow-pain pathway that activates neuron X, this time that collateral cable inhibits the activity of neuron Y. So something painful occurs and activates neuron X, but neuron Y is shut down, making it unable to blunt neuron X. The pain keeps going: chronic, throbbing pain.

In part C, we see the possibility of projections coming down the spine from the brain, which can stimulate or inhibit neuron X. Your brain is influencing how sensitive those neurons are to a painful input. One positive effect of stress can be the blunting of pain perception, which is known as stress-induced **analgesia**. This is shown in part C, via the bottom projection

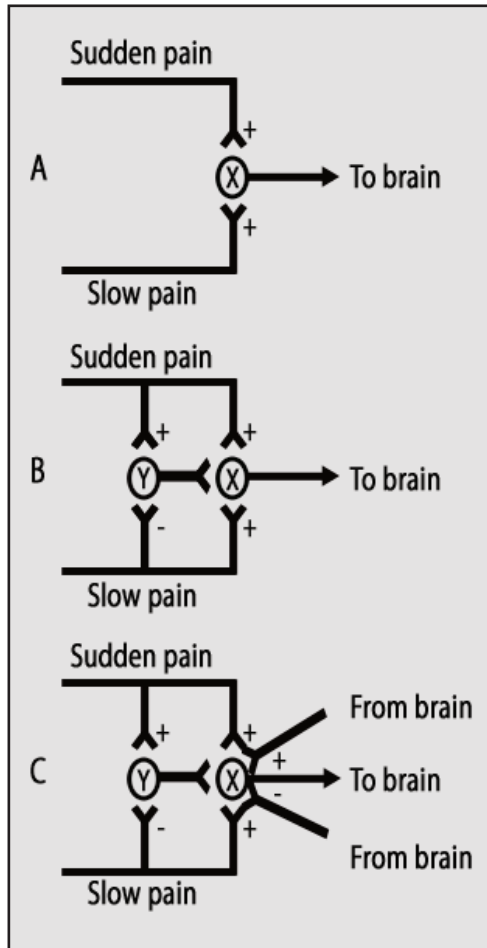


Figure 12.1. The Wall-Melzack model.

coming from the brain. It inhibits neuron X and blunts pain perception, generally with endorphins.

But how does massive, chronic stress impact the pain “wiring” system? Here is the bad news. Major, sustained stimulation of pain pathways makes them more sensitive and more responsive, so that pain begets pain, leading to **hyperalgesia**. You get depleted of beta-endorphin, the hormone that protects you from the stressor. So it is not the case that you eventually turn off the pathways; the pain comes back and just keeps going. ■

Important Terms

analgesia: The blocking of pain perception. Stress-induced analgesia is the phenomenon where extreme, acute stress blocks pain perception.

hyperalgesia: Exaggerated pain sensitivity.

Suggested Reading

Sapolsky, *Why Zebras Don't Get Ulcers*, chap. 9.

Questions to Consider

1. How can stress blunt pain perception (as in stress-induced analgesia)?
2. Why can pain perception be highly subjective?

Stress, Learning, and Memory

Lecture 13

There are a number of different types of [implicit memory]. One example is what would be called fear conditioning, a type of association ... a type of memory, if you will, that your body learns—that you learn implicitly, unconsciously. Let me give you an example of this. I was in the 1989 earthquake in San Francisco, and it was not fun. It left a lasting impression and implicit memory that I often find, which is I might be sitting some place and some large truck rumbles past ... and the ground vibrates a little bit. I stop in my tracks wondering is this another earthquake. What that is is implicit fear conditioning because what occurred during the earthquake was 15 seconds or so of the stimulus, 15 seconds that has taught my implicit pathways something indelible.

How does memory work? There are many different types of memory, and the most relevant to the area of stress and learning is the dichotomy between explicit and implicit memory. Explicit (or declarative) memory is where you know a fact, and you know that you know the fact: I have a birthday in April; I am a mammal. You know the facts sufficiently so that you can actively, consciously behave with that knowledge. In contrast, implicit memory involves things that have been internalized by your body and do not require conscious thought.

What parts of the brain are involved in learning and memory? The hippocampus is intensely involved in memory formation. The **hippocampus** and the associated cortex do the declarative memory type of learning, whereas the cerebellum is involved in implicit memory. What's going on at the level of individual cells? A memory isn't about a new neuron or about a new connection, as previously believed. It's about strengthening preexisting connections, making those connections more excitable, potentiating those connections, and potentiating them so that they last long term. This is called **long-term potentiation** and is the dominant model in the field.

A level that has come to be really interesting to researchers in the field is the notion of networks of neurons storing memory. The whole notion of

In the short term, stress does great things for your learning and memory.

these networks is that information is diffusely distributed. Information of memory is not contained in any single neuron or any single connection; it is contained in patterns of activation. When you are at a party, and you are trying to remember someone's name, you try to pull out that memory by association. How many syllables does that person's name have? I remember it started with a B sound. Where was I when I learned that person's name? Who was I

with? You are tapping into associations, and somewhere at the intersection of all those networks, that name will suddenly pop out.

What then happens with stress? In the short term, stress does great things for your learning and memory. You increase your heart rate, you loosen up blood vessels in critical areas of the brain, you deliver more oxygen and glucose to the brain, and your brain starts working better. Also with the onset of stress, connections between neurons become more excitable in the hippocampus, and long-term potentiation happens more readily. Studies show that stressors make it easier to remember certain things.

With more chronic stress, we begin to see memory disruption. Once stress goes on for a few hours, you are no longer delivering more glucose and oxygen to the brain; you're delivering less. You are no longer enhancing long-term potentiation; you're disrupting it, and in the worst place, the hippocampus. Perhaps most remarkable, with more sustained stress, you change the structure of neurons in the hippocampus; you cause them to atrophy. This makes it harder for neurons in the hippocampus to survive things like a stroke or a seizure. So chronic stress can potentially worsen neurological outcomes. ■

Important Terms

hippocampus: A part of the brain's limbic system that is centrally involved in learning and memory and highly sensitive to the effects of stress.

long-term potentiation (LTP): An increase in the ease with which neurons communicate with each other across synapses; this increase in excitability is thought to be a cellular building block of memory formation.

neurogenesis: The generation of new neurons. The fact that this can occur in the adult brain has been a revolution in neurobiology.

Suggested Reading

Sapolsky, *Why Zebras Don't Get Ulcers*, chap. 10.

Questions to Consider

1. On the level of individual cells and synapses, how does short-term stress enhance learning and memory?
2. On the same level, how does chronic stress do exactly the opposite?

Stress, Judgment, and Impulse Control

Lecture 14

What does the frontal cortex do? It does all sorts of complicated things, regulating executive behaviors and strategizing. ... It makes you do the harder thing when it's the right thing to do. It makes you do something that is difficult when that's what you should be doing. ... For example, the frontal cortex makes you, at a party, do the right thing even though it's harder. You have been served the most horrendous meal you can ever imagine, and it's your frontal cortex that kicks in and says, "Whoa, this is delicious. I've got to have the recipe." It keeps you constrained. It keeps you in line.

It has been demonstrated in rodents and nonhuman primates that massive amounts of exposure to stress or glucocorticoids can actually kill neurons in the hippocampus. But what about in humans? Can sustained stress make neurons in the human hippocampus more fragile, or even kill them? Much of this is impossible to study in humans, because you can't tell if individual neurons are atrophying or whether there is long-term potentiation. But we can use brain-imaging techniques to see the size and level of activity of different structures of the brain. These studies have begun to provide some pretty disturbing conclusions.

This first domain of humans who have excessive exposure to glucocorticoids is those who take synthetic glucocorticoids to control medical problems like lupus or rheumatoid arthritis. The first hints of the literature are showing that these individuals have memory problems that increase with the level of glucocorticoid exposure. The next area of relevance to humans is **Cushing's syndrome**, a number of diseases whose commonality is the secretion of high levels of glucocorticoids. This leads to atrophy of the hippocampus and resultant memory problems. This is almost certainly the atrophy of individual neurons, because laboratory studies show that with the abatement of stress, the processes grow back.

There is emerging literature showing that chronic major depression can be associated with hippocampal atrophy. **Post-traumatic stress disorder** has

also been shown to cause a loss of volume of the hippocampus—and the more severe the traumatic history, the greater the memory problems. What about more everyday stressors, such as chronic occupational stressors? There was a remarkable study done some years ago in which, controlling for all other variables, those folks with more stressful jobs tended to have a smaller hippocampus and greater memory problems. So this is some initial evidence that occupational stress can have some of the same consequences.

Your brain is not just good for learning and memory. Your brain is also good for judgment, for impulse control, for executive decisions—and all of this involves a part of the brain called the **frontal cortex**. The frontal cortex is arguably the most human part of the brain. It does all sorts of complicated things, like regulating executive behaviors and strategizing. The frontal cortex is the last part of the brain to fully develop, a process that takes until around age 25. That explains an awful lot of college campus behavior. It also motivated the U.S. Supreme Court decision that a person cannot be executed for a crime they committed under age 18. There's another realm in which brains don't have much frontal function: brains that have been damaged. A substantial percentage of people on death row in the United States have a history of major concussive trauma to the front of the brain.

What does stress do to the frontal cortex? A lot. The hippocampus and the frontal cortex have glucocorticoid **receptors** at far higher levels than elsewhere in the brain, and sufficient amounts of stress and glucocorticoid excess begin to interfere with how the brain works. It is a very new literature that's just emerging, but it tends to show atrophy of neurons in the frontal



© Creatas/Jupiterimages/Thinkstock

Brain-imaging technology has allowed us greater understanding of the function of different brain regions.

cortex and the layers of the frontal cortex thinning out. What happens after the stress is over with? What's known at this point is that with stress glucocorticoids, there is atrophy of the neurons. After stress subsides, they grow back, but with different sorts of connections. We don't know yet the full significance of these findings. ■

Important Terms

Cushing's syndrome: A collection of diseases involving pathologically elevated levels of glucocorticoids.

frontal cortex: The brain region involved in decision making, impulse control, long-term planning, and gratification postponement.

post-traumatic stress disorder (PTSD): A psychiatric disorder comprising a constellation of symptoms (e.g., sleep disruption, flashbacks, and hypersensitivity to stimuli) caused by severe trauma (e.g., combat trauma, childhood abuse, or rape).

receptor: A hormone or neurotransmitter carrying messages from one cell to another. Each type of hormone or neurotransmitter binds to a specific receptor on a target cell and exerts its actions through that route (e.g., estrogen stimulates uterine growth by binding to estrogen receptors in uterine cells).

Suggested Reading

Spapolsky, *Why Zebras Don't Get Ulcers*, chap. 10.

Questions to Consider

1. What psychiatric disorders are associated with atrophy of the hippocampus, and why might that be?
2. What does the frontal cortex have to do with stress making you more impulsive?

Stress, Sleep, and Lack of Sleep

Lecture 15

We all know this phenomenon, which is you study something right before you go to sleep, you practice a piece of music, or whatever, and the next morning, it's magically in there to a much greater extent than if you had done that same learning in the morning and tested it toward late afternoon. There's consolidation of memory that goes on in the brain during that time.

Sleep is a weird thing to have happen to your body and your brain. Not only is sleep this weird suspended state, but it's very structured, with many different sleep stages. What is going on in your brain when you are sleeping? It depends on which of the sleep stages you are in. Typically when you are sliding into a good night's sleep, the first thing that kicks in is **slow-wave sleep**, so called because the brain has very slow cycles of activation. Most of your brain has much less activity going on, which allows for restoration of energy in your nervous system. Then comes **rapid eye movement (REM) sleep**, during which some parts of your brain become completely silent while others become more active than usual.

Which areas of the brain become more active than usual during REM sleep? One interesting one is the secondary sensory cortex. When you look at something, the information goes into your primary visual cortex. It gets processed there, you extract some information about what's going on, and then you kick that up to your secondary and tertiary visual cortices, which do all sorts of processing. Something different happens during REM sleep: The primary sensory cortex goes silent, and the secondary and tertiary



Sleep is an important factor in combating stress.

© Pixland/Jupiterimages/Thinkstock

become extremely active. In other words, those parts of the brain are processing things without any actual visual or auditory information coming in: This is dreaming.

Why is it that we dream anyway? Why is it that we have any of these sleep stages? And most broadly, why do we need to sleep at all? The answer is somewhat obvious in that sleep restores energy, particularly to your brain.

The brain constitutes about 3% of your body weight, but it uses 20%–25% of your body's energy.

The brain constitutes about 3% of your body weight, but it uses 20%–25% of your body's energy, and brain cells (neurons) have virtually no capacity to store energy. So sleep is especially about restoring energy to the brain. It's only in recent years that people have figured out there's an additional function: You consolidate memories during your sleep. As for why we dream, there have been innumerable theories over the years.

One of the more convincing explanations is that it's a chance to use circuits in your brain that you may have underused during the day. It's not quite clear exactly why we dream, but what is clear is that sleep in general is good for consolidating memory, and REM sleep appears to be particularly useful. If you disrupt REM sleep, you interfere with cognition: You don't remember things as well, and you generally don't learn things as well.

Let's superimpose stress on top of this. Very simply, sleep deprivation is a stressor. If you don't get enough sleep, your levels of glucocorticoids go up. There's a hormone called corticotropin-inhibiting hormone that seems to inhibit activation of glucocorticoids. In other words, it's a hormone that helps the onset of sleep. The very chemical messenger that transitions you into sleep is the same one that decreases glucocorticoid levels. If you don't get enough sleep, your glucocorticoid levels go up, and elevated glucocorticoid levels disrupt sleep. But don't panic—this cycle is not as vicious as it seems. When you are sleep deprived, glucocorticoid levels go up, but not that much. And no matter how high your glucocorticoid levels are, if you're exhausted enough, you're eventually going to sleep. All sorts of other regulatory factors have some input as to how much sleep you get, and they can eventually override the effects of stress. What about the impact of stress on the quality

of sleep? Here there is some particularly disturbing news. You can get lots of sleep, but if there's not a predominance of slow-wave sleep, you don't get the energy restoration that you need. ■

Important Terms

rapid eye movement (REM) sleep: The sleep state during which dreaming occurs. It unexpectedly involves higher levels of activity in some brain regions than during normal waking.

slow-wave sleep: The deepest stage of sleep, in which the most energy restoration occurs. This is the sleep stage most disrupted by stress.

Suggested Reading

Dement, *The Promise of Sleep*.

Sapolsky, *Why Zebras Don't Get Ulcers*, chap. 11.

Questions to Consider

1. Vicious cycle part 1: How do elevated stress hormone levels make it difficult to sleep?
2. Vicious cycle part 2: How does sleep deprivation elevate stress hormone levels?

Stress and Aging

Lecture 16

The picture of aging, it's wonderful. When it works right, you become wise, you become peaceful, you become self-actualized, you wind up looking like Jessica Tandy or someone, and it's all great. As far as I can tell, I am not hurdling in that direction at all. I do not anticipate being wiser, calmer, any of that. Instead, I suspect I'm going to be paying the price of way too much agitated stress throughout the years. What this lecture is about is trying to look at the actual science underlying that distressing outcome.

What is aging about? Your body begins to fall apart after a certain time of life; you become increasingly fragile. You have all sorts of advantages earlier in life that increase evolutionary success, that is, increase the number of copies of genes you pass on. There's no free lunch; eventually the bill comes. There's even a technical term for this—negative pleiotropy, the notion of some genetic trait that gives you advantages earlier in life at the cost of disadvantages later on.

Where does stress intersect with aging? From virtually the day the concept of stress was identified in the 1930s, people have theorized that stress and aging must be intertwined in some basic way. This theorizing took 2 forms. The first one is that aging is a time of life when organisms don't deal with stress very well. The second is that lots of stress throughout the lifetime will accelerate the aging process. It seems we've got another vicious cycle on our hands: Lots of stress makes you get older faster, and being older and more fragile can make you less able to deal with stress.

What's the evidence for these 2 ideas? There is endless evidence for the first one at all different levels of body functioning: Aging is a time of life when you don't deal very well with stress. Naturally what we want to do is translate this into one of our greatest markers of stress: What happens to glucocorticoid levels as we get older? They stay reasonably flat until extreme old age, and then they take off. The stress-response, the amount of glucocorticoids you could pump out in response to a stressor, doesn't

change a whole lot during aging. What does change is the recovery time, how long it takes to get back to baseline. These elevated glucocorticoid levels in old age decrease the rate of neurogenesis in the hippocampus. So aging is a time of life where you don't deal very well with stress, and you pay a price: decreased DNA repair, decreased ability to regulate temperature, and decreased cognitive ability.

Not only is aging a time of life when you don't deal very well with stress, but lots of stress over the lifetime can also accelerate the aging process.

It turns out there's plenty of support for the second of these twin theories as well: Not only is aging a time of life when you don't deal very well with stress, but lots of stress over the lifetime can also accelerate the aging process. There is substantial literature supporting the notion that a history of lots of stressors accelerates the cognitive decline of aging. Some examples of this can be found in topics covered earlier in this course.

In the research in which experimenters picked up baby rats and neonatally handled them, it was seen that as long as the handling was for a very short period, after the baby was returned, the mother was more attentive. It was also found that these rats have a much more successful old age, that in their old age, they haven't lost as many hippocampal neurons. Their cognition is better, and their overall health is better. The Dutch Hunger Winter fetuses are another example. Their prenatal starvation led to a thrifty metabolism, which hurdled them at a significantly higher rate toward diseases that are more common with aging: metabolic syndrome, obesity, hypertension, and diabetes. This does not only apply to prenatal stress: Stress throughout the lifetime increases the likelihood of and accelerates the progress of metabolic diseases of aging. ■

Suggested Reading

Kirkwood, "Healthy Old Age."

Spolsky, *Why Zebras Don't Get Ulcers*, chap. 12.

Questions to Consider

1. What is the evidence that aging is a time of life when organisms are less capable of dealing with stress?
2. What is the evidence that stress can accelerate aspects of aging?

Understanding Psychological Stress

Lecture 17

You get a baboon who has just had a scare, a lion has almost gotten him, and what does he do afterward? He runs over and grooms somebody. You get the entire troop where something scary has happened, some lion has leapt out and everybody just barely made it into the trees, and when the lion is gone, everybody comes down and sits and grooms for the next half hour. It is very socially calming.

What is it that determines how stressful psychological stressors will be? There are some very powerful psychological factors that modulate the stress-response. The first one is whether you have an outlet. In work pioneered by Jay Weiss, then at Rockefeller University, he would take a rat and shock it every now and then. With enough of these, the rat would develop an ulcer. Then he took a second rat. Every time the first rat got a shock, so did the second, with the same intensity, duration, everything, except one critical difference: Every time that second rat got a shock, it could go over to a bar of wood and gnaw on it with its teeth. That second rat would not get an ulcer. It had an outlet for the frustration caused by the stressor. It soon emerged that all sorts of outlets worked for rats under those conditions: going into a running wheel and running off the stressor, overeating—all of these would wind up protecting from a stress-related disease.

What about in humans? Are stressors capable of being modulated by outlets? We have hobbies; we work off tension in the gym; we scream in the stairwell after that stressful meeting. Why should physical outlets reduce the stress-response after a stressor? For a number of reasons. First, they release muscle tension, especially if it is a psychosocial stressor. Next, they distract you; that's what some of the most basic human hobbies are about. They can also work because they can remind you of what's really important in life. For example, at the end of your long day of traffic, striving, ambition, and shallow wishing, you can come home and have the outlet of playing with your children.

There's one type of outlet that pops up frequently and is really distressing. If the first rat is allowed, after getting its shocks, to run over to the other side of the cage and bite a second rat, guess what happens? The rat doing the biting does not get an ulcer; it is carrying out displacement aggression onto an innocent bystander, and disturbingly, this works very well. This is why during periods of economic duress, rates of family violence go up. Displacing aggression onto an innocent bystander is one of the most common and efficacious things that social organisms do to feel less stressed.



© iStockphoto/Thinkstock

Studies on rats have shown that having an outlet is a great mitigator of stress.

But there is a more positive factor that affects stress outcomes. Take that first rat, but now after the shocks, let it run over to the other side of the cage where there's a rat that it knows and likes. They groom each other, and the first rat doesn't get ulcers. This is social support. If the second rat is a complete stranger, the logical thing to do is displace aggression on it. But if it's a rat the first one knows, it grooms it, which is protective and is stress reduction.

What does this look like in humans? This is the whole world of social affiliation. It's also pertinent in all sorts of very acute circumstances. Take somebody going through a short medical procedure that's kind of stressful. Have somebody there who they know and like to hold their hand, and their stress-response is decreased. Social support is a highly protective factor.

The next factor is predictability. If the rat sees a little warning light 10 seconds before each shock, it doesn't get an ulcer. Predictive information is enormously powerful. If you know when something bad is coming, how bad it is going to be, and how long it is going to last, you can plan coping strategies. This is the principle behind one of the most central questions any of us might ever ask, which is, how much time do I have left? ■

Suggested Reading

Sapolsky, *Why Zebras Don't Get Ulcers*, chap. 13.

Questions to Consider

1. What sort of findings made stress a subject of interest to psychologists as well as to physiologists?
2. What are 2 key psychological modifiers of the stress-response?

Psychological Modulators of Stress

Lecture 18

They looked at patterns of stress, subjective senses of stress, health, all of that in 2 groups of musicians, those playing professionally in symphony orchestras and those playing professionally in small ensembles, string quartets, and things of that sort. What they saw was the chamber music folks were far less stressed. What's this about? ... [There] is a miserable lack of control on the part of the instrumentalists in [orchestras] because the conductor controls everything. It was, in fact, until not that many years ago the unions of orchestral musicians got the right to demand bathroom breaks with some regularity.

What is it about psychological stress that is stressful? We covered 3 key variables in the last lecture—outlets for frustration, social support, and predictability. Another major factor is a sense of control. As a general rule, the more of a sense of control you have, the less stressful the stressor is.

A major area of focus in this field is the amount of control people have in the workplace. Who do you see getting stress-related disease in the corporate world? It's not upper management, as previously believed; it's middle management. A key feature of life in the middle is you have high demand and low control—high demand in that you're in a position of great responsibility, low control because you're not the one making policy. Second on the list of bad work scenarios are ones with the combination of low demand and low control, because these people have a lack of control plus boredom. For the folks in upper management, as long as they are doing a job that they like, the high degree of control and high degree of demand make a great combination.

The next variable is more subtle: the perception of whether things are getting worse or better. Here's a possibility in a corporation: A worker in the mailroom is making \$7 an hour while the CEO is getting a gazillion dollars a year. People suddenly discover that the mailroom person is the most skillful mailroom person on the entire planet, and management

decides to reward this. Starting tomorrow, he will have \$100,000 a year salary. Meanwhile, the CEO has done some disastrously imprudent things and practically bankrupted the company. She is told she too will have

For the folks in upper management, as long as they are doing a job that they like, the high degree of control and high degree of demand make a great combination.

\$100,000 a year salary. You can bet that \$100,000 a year means very different things depending on which direction you're coming from.

So how can we live our lives successfully with what we've learned in these 2 lectures? If you think the rule is to get as much control in your life as possible, get as much predictive information as possible, and have as many outlets as possible, that's actually not going to reduce your levels of stress. That's going

to increase it in lots of ways because it turns out these principles don't apply all the time; they apply only with certain parameters. Predictive information only works during a certain window—it is of no use when you don't have enough time to activate a coping strategy, and having it too far in advance for a major stressor can actually makes things worse. The nature of the predictive stressor is also a factor: Predictive information helps only for stressors with a moderate likelihood of occurring. It doesn't help in cases of a stressor so rare that you don't even worry about it or a stressor so common that you take it for granted.

So predictability helps only some of the time. How about a sense of control? The easy conclusion to draw is that you should have as much of a sense of control as often as possible. In reality, a sense of control can be a disaster at times. One of the most compassionate things we ever do is to try to decrease somebody's sense of control: "Nobody could have stopped the car in time, the way that little girl darted out." We let people know there's nothing they could have done about it; it's not their fault. One of the worst things that we ever do is magnify somebody's sense of control: "What do you expect if they refuse to assimilate into society? Of course people are going to turn against them."

What have we learned about stress and control? In the face of stressors that are mild to moderate in severity, you want to increase a person's feeling of control, whether it's realistic or not. It feels great; it builds up a sense of efficacy. In the face of disastrous stressors, you do not want to inflate a person's sense of control, because you're setting him up to think that he failed. ■

Suggested Reading

Sapolsky, *Why Zebras Don't Get Ulcers*, chap. 13.

Questions to Consider

1. When is (and isn't) a sense of control stress-reducing?
2. When is (and isn't) information about an impending stressor stress-reducing?

Stress and the Biology of Depression

Lecture 19

As I said before, I think major depression is among the worst diseases that can possibly happen to you, and it's because of this main symptom. Think about a remarkable feature of humans. You get somebody with a nightmare of a disease, with cancer, terminal cancer. To a surprising extent people will wind up saying things like, "Obviously I didn't want this disease and don't want to die, but it wasn't until I got the cancer that I realized how important family is to me, or what good friends I have, or I found my God, or, I almost feel grateful for it." We humans have this bizarre ability to find pleasure in the most unlikely places, and the defining symptom of depression is ... you lose the capacity to feel pleasure.

This and the following lecture are devoted to major clinical depression. We devote so much time to depression because it's a complicated subject and because it affects so many people. Current estimates by the World Health Organization are that depression is the fourth leading cause of disability in the world. By 2020, it is expected to be in second place, after metabolic syndrome.

What are the symptoms of depression? The core symptom is **anhedonia**, the inability to feel pleasure. Many people with depression experience grief and guilt so severe that they begin to distort the way they interpret the world around them. There is also the tendency of people who are highly depressed to injure themselves, to attempt suicide, or to succeed at committing suicide. Many experience social withdrawal, loss of libido, and changes in sleep patterns. The tendency is to fall asleep fairly normally but wake up very early in the morning. The architecture of sleep patterns is disorganized in people with depression; their brains work differently. There are also changes in appetite and in many aspects of metabolism. In a substantial percentage of sufferers, there are increased levels of glucocorticoids, which means stress, and which also indicates that depression is a biological disorder. Another feature of the disease also screams biology: the fact that there are patterns to when people have their depressions. The most striking example of that

is people who get depressed only at a certain time of year, typically the winter months.

What is wrong biologically in depression? First let's look at how brain chemistry works. The figure below shows the basic flow of information between 2 neurons (or brain cells). One neuron sends a projection to another through a small space in between called a **synapse**. The first neuron releases a chemical messenger, which floats across the synapse. The messenger comes out of the extreme end of the neuron, called the axon terminal, and floats across a tiny distance to the dendrites of the next neuron, allowing it to interact with its neurotransmitter receptor. The neurons talk to each other by way of these neurotransmitters, leading to a change in the second neuron, such as it becoming more excitable.

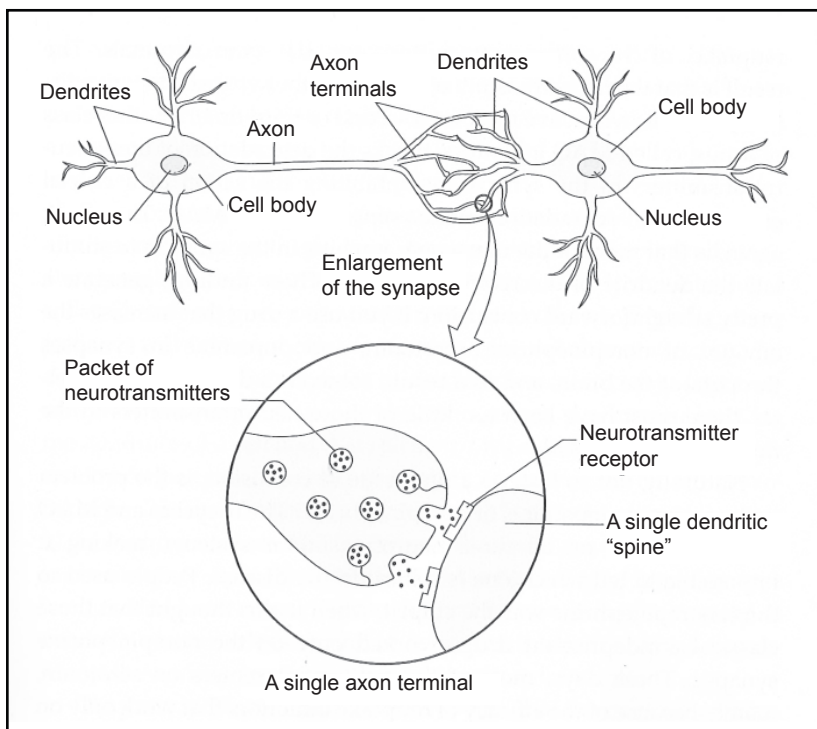


Figure 19.1. The functioning of brain chemistry.

There are many different chemicals that appear to be neurotransmitters. What is happening with the neurochemistry of depression? Here is an extremely simplified summary of what we know now: **Norepinephrine** has to do with energy; so the absence of norepinephrine begins to explain the psychomotor retardation of depression—how it feels exhausting to do everything. **Serotonin** has to do with the rumination on grief, despair, and guilt. And the shortage of dopamine has to do with the anhedonia. What about the neuroanatomy of depression? A depression is when your frontal cortex, in particular a subarea called the anterior cingulate, comes up with abstract sad thoughts and manages to get the rest of your brain to go along with it as if it were a real stressor. So we have demonstrated that this is a biological disorder, as biological as diabetes, but we see in the next lecture that if we only look at the biology, and do not focus on the psychological aspects as well, we are not going to be in a position to help someone who is clinically depressed. ■

Important Terms

anhedonia: The inability to feel pleasure; a defining symptom of depression.

norepinephrine (a.k.a. **noradrenaline**): A type of neurotransmitter closely related to epinephrine. There is good evidence that its release in one region of the brain is blunted in depression; in a different part of the nervous system, it plays a central role in the sympathetic nervous system (along with epinephrine).

selective serotonin reuptake inhibitor (SSRI): Any of a class of antidepressants (e.g., Prozac) that increase serotonin signaling in the synapse by blocking their reuptake (i.e., removal) from the synapse.

serotonin: A type of neurotransmitter. Of greatest relevance, evidence suggests that a shortage of serotonin in some brain regions contributes to depression.

synapse: The microscopic gap between the branches of two neurons; excitation in one neuron leads to the release of specific neurotransmitters,

which float across the synapse, bind to specialized receptors, and alter the function of the other neuron.

Suggested Reading

Cohen, Janicki-Deverts, and Miller, “Psychological Stress and Disease.”

Sapolsky, *Why Zebras Don't Get Ulcers*, chap. 14.

Questions to Consider

1. What sort of evidence shows that depression is as biological a disease as diabetes is?
2. What does stress do to the brain chemistry that is most relevant to depression?

Stress and the Psychology of Depression

Lecture 20

Men and women have the same rates of bipolar; women have roughly twice as much diagnosis of unipolar depression. What's that about? All sorts of possibilities, all sorts of theories. One is the diagnostic criterion problem, which goes as follows: Men, when depressed, are more likely than women to self-medicate themselves with alcohol, with various drugs, and they're more likely to be labeled as an alcoholic than as a depressive. There's not actually difference between men and women, it's just that a lot of the men get categorized in another way.

The previous lecture covered a number of aspects of the biology of depression. What about hormones; what do they have to do with depression? It turns out a whole lot. On average, women have higher rates of depression than men do, and the risk of depression in women tends to peak at certain times in life: during the 2 weeks after giving birth, around menopause, and around one's period. These are all circumstances where there are very dramatic changes in levels of certain hormones. Two of the most pertinent ones, estrogen and progesterone, have a great effect on the brain. The next one that comes in is **thyroid hormone**, which plays a large role in maintaining your metabolic rate. When people become hypothyroid, they have a greatly increased risk of falling into a depression. In fact, the numbers suggest that something like 15%–20% of depressions are not due to a primary depressive disorder but instead are secondary to an undiagnosed hypothyroidism.

What's the evidence to think there's a link between stress and depression? The first is epidemiological: People who have just had major stressful events are statistically more likely to fall into a depression. Furthermore, people who are given high levels of synthetic glucocorticoids for autoimmune disorders or inflammatory issues have greatly increased risk of going into a depression.

At this point, we know a bit about the neurochemistry, the brain structure, and the endocrinology—but we are not going to be very good at curing

depression. To begin to put the pieces together, we now have to transition from depression as a biological disorder to looking at the psychological aspects of depression.

Sigmund Freud had some remarkably insightful things to say about depression. Freud wrestled with figuring out the difference between mourning and melancholia, that is, a reactive, transient depression and a major clinical depression. The core of Freudian thinking is that whom or what you love, you also hate; there is this ambivalence. In this view, depression comes out of a circumstance where you lose something or someone whom you loved, and there is hatred and ambivalence mixed in. Freud posited that in the aftermath of this loss, if you were able to put the anger and resentment aside and focus purely on the sadness, the love, the loss, you get simple mourning. If instead you can't put the hate aside, you have melancholia, major depression.

It's at the intersection of the organic basis and the psychological (or psychosocial) basis of a disease that we get the most insight, and very frequently, that intersection is about stress.

We learned earlier the key building blocks of psychological stressors: lack of outlets, lack of control, lack of predictability, lack of social support, and the perception that things are worsening. A depression, in a sense, is a pathological extreme of those perceptions. This fits with the fact that a child who loses a parent to death at an early age is permanently at greater risk for depression. A lot of childhood is about learning what things you can control and what things you can't. When you learn not only that there are things that you can't control but also that some of them are incredibly awful, you begin to learn in an overgeneralized way that you don't have much control over anything. This sets you up for the cognitive distortion that this is what life is like. This is **learned helplessness**.

This is a powerful model and one that I think gives us the most insight into the psychology of depression—depression as caused by extremes of psychological stress. We've got 2 very different views—the neurobiology

and the experiential cognitive distortion—and we begin to fit them together in an elegant way that’s built around stress. We have seen the intertwining of the two—the role of stress as impacting the biology of depression and the role of stress as an outcome of certain adverse aspects of your life. This brings us back again to an absolutely critical point: It’s at the intersection of the organic basis and the psychological (or psychosocial) basis of a disease that we get the most insight, and very frequently, that intersection is about stress. ■

Important Terms

learned helplessness: A term often used in the context of depression, describing a state where an individual, due to repeated psychological stress, has lost the capacity to recognize circumstances where it is possible to effectively cope with a stressor.

psychomotor retardation: A key symptom of major depression, in which thought and action seem exhausting.

thyroid hormone: Secreted by the thyroid gland, its main function is to increase metabolism. Abnormally low thyroid hormone levels (i.e., hypothyroidism) can give rise to depression.

Suggested Reading

Cohen, Janicki-Deverts, and Miller, “Psychological Stress and Disease.”

Sapolsky, *Why Zebras Don’t Get Ulcers*, chap. 14.

Questions to Consider

1. What does the phenomenon of learned helplessness have to do with depression?
2. Where do neurobiology, psychology, and genetics intersect in making sense of depression?

Anxiety, Hostility, Repression, and Reward

Lecture 21

There're ... different genetic versions of dopamine receptors, some of which are less responsive; you need more of an umph in the system to keep it from habituating. To appreciate this, think about this, who is that guy? Evel Knievel, that was that madman who would motorcycle over all sorts of like cruisers and things of that sort and had broken every bone in his body over and over. You think about it, once a long, long time ago the young Evel Knievel, who had his driver's permit in his back pocket, raced a red light, just got across in time and got a little bit of a thrill from that. The next day, that wasn't enough.

This lecture examines more areas in which major stress has psychiatric implications. The first one, anxiety, is a psychiatric disorder that affects perhaps even more people than depression. To understand the biology of anxiety, we look at a part of the limbic system called the **amygdala**. The amygdala plays a role in learning to be fearful of new things and in innate fears and phobias. What does stress have to do with this? On a purely behavioral level, stress increases anxiety. The amygdala is extremely sensitive to glucocorticoids. With sustained stress and lots of glucocorticoids, the amygdala gets better at doing what it does, which is learning to be afraid. Its synapses become more excitable, and it can even grow new processes. The neurons get larger and more interconnected, setting you up for an anxiety disorder.

A second realm related to stress is hostility, which used to be called **type A personality**. **Toxic hostility** is a personality style where you think anything that happens around you is proof that everyone is out to get you; you have to watch your back 24-7. You're in the supermarket, and you've picked the slower line. You want to kill the idiot kid behind the cash register for intentionally slowing you down. You're thinking, "Come on, come on, come on!" Instead of checking out the People magazines, you drive your blood pressure up and put yourself more at risk for cardiovascular disease.

A third realm of intersection between personality and stress is that of repressive personalities, which are held by about 5% of the population. By definition, if you are repressive, you don't have depression or an anxiety disorder—in fact, you tend to be really happy. These are the folks who are highly organized and have everything under control. They walk the

By definition, if you are repressive, you don't have depression or an anxiety disorder—in fact, you tend to be really happy.

same way to work every day and can tell you what they're having for dinner 2 weeks from Thursday. They have a lot of discipline and get tons accomplished. Everything is terrific—until something stressful comes along, because they don't deal well with ambiguity or surprises. There are some downsides to it, but

these are people who are normally highly functional, very productive, and happy. What is happening in their bodies? The level of metabolism in their prefrontal cortex is above normal, and their bloodstream has elevated levels of glucocorticoids. This makes an important point, which is sometimes it can be enormously stressful to create a world in which nothing stressful ever occurs: There's chronic activation of the stress-response in repressive individuals.

The goal of research in this area is not to get rid of stress. We don't want lives without stress whatsoever; in fact, stress is great when it's the right kind. The right kind of stress is called stimulation. Ask somebody who works in child development or gerontology, and they'll tell you people need stimulation. What counts as stimulatory stress? A moderate stressor that doesn't go on for too long and that you experience in a safe context.

We have entered this terrain of stress, under the right parameters, being pleasurable. What goes on in the brain to explain it? A neurotransmitter called **dopamine**. Dopamine is about reward, or more accurately, the anticipation of reward. It's also about the motivation that comes out of that anticipation. What happens with moderate amounts of stress that are moderately transient, with moderate increases in glucocorticoid levels?

You increase the release of dopamine. Short-term stress improves those aspects of mood; chronic stress depletes you of dopamine, and thus, you have less of a capacity for pleasure or the anticipation of pleasure. ■

The Delayed Discovery of Type A Personality

Here is the fascinating story of how type A personality was first discovered, which I got from the horse's mouth some years ago. Meyer Friedman, the cardiologist who first described it, died a few years ago at age 91. In the 1950s, he and his partner had a new cardiology practice; everything was going fine. But they had this one problem, which was that for some weird reason the armchairs in the waiting room were getting worn out at a very high rate.

Every month the upholsterer would come and fix a couple of the chairs. One month, the upholsterer was on vacation; the replacement upholsterer comes in, takes one look at the chairs, and discovers type A personality. He says, "What's with your patients? Nobody wears out chairs this way." That was indeed the case: The front 2 inches of the seat cushions and the front 2 inches of the armrests were totally shredded. This is the type A profile—people who are literally sitting on the edge of their seat, squirming and clawing nervously. This is what type A individuals look like when they have heart disease and are sitting in the office of their cardiologist. This is what it was.

What happened next? This is where things get really unfortunate. At that point Dr. Friedman should have grabbed the guy and said, "Good God, man, what you've discovered!" But that didn't happen. What happened instead? Dr. Friedman told his nurse, "Get this man out of my face. I'm an important cardiologist; he's wasting my time." Dr. Friedman himself was too type A to listen to the guy. It was about 5 years later that the doctor was collaborating with some psychologists and the type A profile popped up, and they said, "Oh my God, the upholsterer—he was right." To this day, nobody has a clue who that man was. This stands as one of the truly dark chapters in the history of science and medicine.

Important Terms

amygdala: A part of the brain's limbic system that plays an important role in fear and anxiety.

dopamine: A type of neurotransmitter whose numerous functions include a role in anticipation of pleasure; abnormalities in it have been found in individuals with depression.

toxic hostility: A personality style where an individual consistently interprets benign events as being threatening and calling for a hostile coping response. This modern incarnation of the type A personality concept carries an increased risk of cardiovascular disease.

type A personality: A personality style first described in the 1950s that carries an increased risk of cardiovascular disease. In its original formulation, type A individuals tend to be highly competitive, overachieving, time-pressured, impatient, and hostile.

Suggested Reading

Nestler and Malenka, "The Addicted Brain."

Sapolsky, *Why Zebras Don't Get Ulcers*, chaps. 15–16.

Questions to Consider

1. What does stress do to the brain that helps explain the increased risk of anxiety?
2. When do we love stress?

Stress, Health, and Low Social Status

Lecture 22

To give a remarkable example of this lack of control [among those with lower socioeconomic status], this was a study in the early '90s, looking at a bunch of men who had problems with hypertension and thus were taking antihypertensive drugs. One particular type is a diuretic. In this study, we show that one of the major reasons why working-class men with high blood pressure would stop taking their antihypertensives was because they had to go to the bathroom more often than they were allowed to on their job.

We have learned that you cannot understand the biology of disease outside the context of the person in which the biology is occurring, and now we see that we must also look at the context of the society in which that individual dwells. What does your place in society have to do with your health, and how does stress factor in?

The one clear-cut human hierarchy in Westernized societies is **socioeconomic status** (SES), and it is clear that being at the bottom of the SES hierarchy is bad news. For one thing, you're subject to more physical stressors: You have to haul the groceries upstairs because you live in an old building where the elevator is broken; you have to walk further with the heavy groceries because your car isn't working; you have to do manual labor for a living. The realm of psychological-psychosocial stress is disproportionately focused on the poor as well. You have a relative lack of control—you spend your life working on an assembly



© Felipe Dupuy/Lifesize/Thinkstock

Individuals with lower socioeconomic status tend to be exposed to more stressors.

line instead of being in a position of determining your own occupational fate. You have a lack of outlets—you can't join that expensive health club when you're feeling stressed out. Perhaps most important is the fact that you don't have as much social support as wealthier people. You can't do a whole lot of social support if you're working 2 or 3 jobs or spending all your time trying to fix everything around you that is broken.

In the greater Washington DC area, inner-city residents have a 16-year shorter life expectancy than those in the wealthier suburbs.

What does SES have to do with your health? There is something called the SES gradient of health: Across Westernized societies, the poorer you are, the worse your health is. You have higher rates of a whole variety of diseases: cardiovascular

disease, respiratory diseases, psychiatric disorders, metabolic diseases, and vulnerability to diabetes. With some diseases in some societies, there's a 20-fold difference in the incidence of these diseases between those on top and those at the bottom. As one example, in the greater Washington DC area, inner-city residents have a 16-year shorter life expectancy than those in the wealthier suburbs.

What's the cause of this socioeconomic gradient? Numerous studies have shown that about one-third of the variability is accounted for by lifestyle risk factors. Poor people drink more than wealthier people, they smoke more, they eat to excess, and they get less exercise. But what's the remaining two-thirds about? For a while, we didn't have evidence, but stress physiologists suggested it's about stress. Why? In part, it was by default, because other explanations had been eliminated. We also noted that the types of diseases that are most sensitive to stress are the ones that show the steepest SES gradients. Moreover, 100 years ago, there was a completely different set of diseases from today, yet the same SES gradient was there.

In recent years, studies have come through and shown in a major way that stress is the predominant factor in the socioeconomic gradient. A person's objective SES is a predictor of health, and their subjective SES is at least as good. In other words, feeling poor has at least as much impact as being poor.

Another critical variable is how much income inequity a society has. For poor people with the same income, those in countries with greater income inequality have worse health. We can really see here the power of SES to subordinate the health of humans, and to do it in a way that's heavily mediated by stress. ■

Important Term

socioeconomic status (SES): An aggregate measure that incorporates level of education, wealth, and place of residence. Low SES is a predictor of increased risk for a wide variety of disease, as well as for significantly shortened life expectancy.

Suggested Reading

Marmot, *The Status Syndrome*.

Sapolsky, *Why Zebras Don't Get Ulcers*, chap. 17.

Questions to Consider

1. What's the evidence that lack of health-care access has little to do with the socioeconomic status health gradient?
2. What do the distinctions between being poor, feeling poor, and being made to feel poor teach about the socioeconomic status health gradient?

Stress Management—Clues to Success?

Lecture 23

The closest thing our society has to a village elder, being a Supreme Court justice—tremendous longevity, function and quality, and successful old aging in those folks. It makes perfect sense. This is like the world's greatest job. You don't work that much of the year. You only pick the cases that are interesting, all the scut work is done for you by these hyperactive, manic law clerks, and then you decide things that change the course of history. No wonder these guys do wonderfully; it's our equivalent of a village elder.

Thus far, we've had 22 lectures of bad news. At this point, it must seem miraculous that you're still functioning. How is it any of us are still functioning? How have we not all just collapsed into puddles of stress-related disease? We're scraping along; we're coping. It's clear that some individuals deal with stress much better than others, so we begin by looking at what is different about those individuals.

What is one of the big predictors of successful aging? Having a healthy lifestyle. Smoking, being overweight, not getting enough exercise, and drinking too much all shorten your life expectancy. This makes perfect sense. The next thing is to have a long-lasting, good marriage. This too makes sense from everything we have learned about social connectiveness and social support. Other factors are also obvious from earlier lectures: Avoid major clinical depression throughout adulthood, have an extroverted personality, and get treated with respect.



© Stockbyte/Thinkstock

Nursing home residents thrive when given greater responsibility and autonomy.

I know what you're thinking: This doesn't do me much good. I don't have the option to not be depressed or to have the right temperament in the face of cancer or to go back and make sure my mother touched me the exact right amount when I was an infant. What can I do to make use of these principles? One thing that is clear is change can occur. Some individuals with type A personality who suffer a heart attack, with some very intensive work, change their personality profiles.

Some of the deepest insights into our ability to change have come from experimental studies where people have manipulated psychological variables and brought about change. One study with individuals with chronic pain syndrome discovered that when they are allowed to self-medicate, they actually take fewer painkillers. This change medicated the pain—and also the lack of control. Studies done in nursing homes have demonstrated the ability to counter some of the downsides of the aging process—the loss of control, loss of outlets, and loss of autonomy. Something as simple as giving a resident a plant and telling them that they need to remember to water it every day gives the person some responsibility and autonomy. Their energy levels get higher. Often when the conditions of these studies are reversed, the individuals don't just drop down to the level at which they started; they drop lower.

So what have we learned here? Hope can be an amazingly powerful, sustaining set of feelings, but nothing destroys us more like when there's hope that turns out to be utterly unjustified. This gives us a first warning as we transition into the final lecture on how to apply some of these principles to ourselves. What we see is it's not simple; there are double-edged swords all over the place. You want to get it right, because if you apply some of these notions simplistically, you won't help lessen the effects of stress—and you could perhaps even make things worse. ■

Suggested Reading

Monat and Lazarus, *The Praeger Handbook on Stress and Coping*.

Sapolsky, *Why Zebras Don't Get Ulcers*, chap. 18.

Questions to Consider

1. What do baboons, nursing home residents, and parents of cancer patients teach about dealing with stress?
2. What sort of experimental manipulations make an individual more resistant to stress?

Stress Management—Approaches and Cautions

Lecture 24

When you were young, what stress management is about is trying to make the stressor go away. As you get older, what effective stress management is about is learning to adapt to the inevitable. This is a very important difference. This was wonderfully summarized in a quote that I once heard in a Quaker meeting, which is as follows: “In the face of strong winds, let me be a blade of grass. In the face of strong walls, let me be a gale of wind.”

Our challenge here at the end of this course is to begin to take some of those pictures of spontaneous success at dealing with stress, and some of those demonstrations of experimental manipulation that make individuals better at stress, and look at how to apply these principles to yourself. This is a grand overview of components of stress management, and of course it comes with many qualifiers.

The first thing you can do is exercise. Exercise helps in all sorts of ways: It decreases your chance of cardiovascular disease, and that seems to protect against certain aspects of brain aging and cognitive decline. If your cerebrovascular system is not getting gummed up, you are going to have a brain that works better and that ages better. Exercise also stimulates neurogenesis and helps your neurons grow new processes and new connections. The one qualifier to keep in mind about exercise is that if you overdo it, it can negatively impact your reproductive system.

There are certain qualifiers that apply to exercise as well as the other techniques in this lecture. First, you cannot save your stress management for the weekend; it has got to be done virtually daily. Next, you need to take the time out for it. It needs to be something that is important enough to you that you are going to say no to all those stressors competing for your attention. In the realm of aerobic exercise, for example, most studies suggest you need to do 20 to 30 minutes to begin to get the cardiovascular advantages. Last, you have got to like doing it: If a personal trainer is forcing you to exercise, you do not get anywhere near as much of the health benefits.

Transcendental meditation also does great things for you. It lowers heart rate and blood pressure as well as cholesterol levels—in particular, bad cholesterol. What is unclear in that literature is how persistent those effects are. There is also a huge confound in that literature—the problem of self-selection. It is not just anybody who decides to meditate on a regular basis; people who do so are probably already somewhat different from other folks.

What else can you do? You can have social support—people you love and trust.

We have seen how this has a calming effect. There are caveats here, too: In studies on the effects of marriage on the immune system, it was found that for men, getting married improves their immune system. But it is not as simple for women: They don't get a benefit just from marriage; it has got to be a good marriage.

Religious belief tends to increase protection against cardiovascular disease and depression and increase life expectancy. They are not huge effects, but there definitely is some protection. But this is an incredibly controversial field: The effects are hard to measure, there are many different kinds of religious belief, and there is the enormous confound of self-selection bias. Maybe people who are more religious tend to have healthier behaviors. Another confound is that people who are highly religious also have a community of social support. So this is particularly hard to study.



© Erik Snyder/Photodisc/Thinkstock

Exercise can decrease the chance of cardiovascular disease and protect against brain aging and cognitive decline.

Another principle you can use is cognitive flexibility. This means recognizing when your strategy is not working and it is time to do something different. Some of the time, stress management is about tackling the problem; some of the time, it's about realizing that it is not going to go away and you need to accept it. Inevitably this brings us to that famed Reinhold Niebuhr quote, the Serenity Prayer, this notion of being able to accept the things you cannot change, having the courage to change the things that are changeable, and of course having the wisdom to tell the difference between the two. Very few of us are getting stressed because we are running away from saber-toothed tigers. Instead we have this bizarre, cognitively complex, Westernized lifestyle luxury of wallowing in psychogenic stressors. That is really the final point here: In so far as we are smart enough to make these things up and foolish enough to fall for them, all of us have the potential to instead keep them in perspective. ■

Important Term

John Henryism: A personality style where one perceives oneself to have control over circumstances where, in fact, that is not the case. It has been specifically applied to working-class African Americans and is associated with a greatly increased risk of cardiovascular disease.

Suggested Reading

Monat and Lazarus, *The Praeger Handbook on Stress and Coping*.

Sapolsky, *Why Zebras Don't Get Ulcers*, chap. 18.

Questions to Consider

1. What is the role of social support in stress management?
2. When are traditional stress-management techniques—like meditation, religiousness, and exercise—most effective?

Glossary

abdominal fat: Fat deposits around the gut. Chronic stress preferentially promotes the deposition of abdominal fat, which is of the type that is worse for cardiovascular health.

adrenaline: *See epinephrine.*

amino acids: Approximately 20 different kinds of closely related molecules that are the building blocks of protein.

amygdala: A part of the brain's limbic system that plays an important role in fear and anxiety.

analgesia: The blocking of pain perception. Stress-induced analgesia is the phenomenon where extreme, acute stress blocks pain perception.

anhedonia: The inability to feel pleasure; a defining symptom of depression.

anterior cingulate cortex: A region of the brain's frontal cortex that plays a role in evaluating pain and in empathy. Abnormalities in its function have been noted in people with depression.

atherosclerosis: A disease of the vascular system in which portions of the inner lining of blood vessels are degenerated and inflamed and deposits of cholesterol form plaques that impede blood flow.

autoimmune disease: A disease in which the immune system mistakenly responds to a part of the body as if it is an invasive pathogen and attacks it. Examples include juvenile diabetes, in which insulin-secreting cells in the pancreas are attacked; rheumatoid arthritis, in which joints are attacked; and multiple sclerosis, in which aspects of the spinal cord are attacked.

autonomic nervous system: A part of the nervous system that mediates aspects of the body's function that are often automatic, or involuntary. Consists of the sympathetic nervous system (generally involved in arousal and stress-responses) and the opposing parasympathetic nervous system (generally involved in calm, vegetative bodily function).

benzodiazepines: Anxiety-reducing tranquilizers such as Valium and Librium. The brain contains receptors for them, indicating that the brain makes still-undiscovered natural versions of these drugs.

beta-endorphin: A hormone released during stress, predominately from the pituitary gland. It plays a role in stress-induced analgesia and in some of the disruptive effects on reproduction.

cholesterol: For the purposes of this course, there is “bad,” LDL (low-density lipoprotein) cholesterol, which promotes atherosclerosis, and “good,” HDL (high-density lipoprotein) cholesterol, which does the opposite.

cortex: The outer surface of the brain, it is the most recently evolved and involved in the most abstract brain functions. Most pertinent to this course is the frontal cortex.

cortisol: *See glucocorticoids.*

Cushing's syndrome: A collection of diseases involving pathologically elevated levels of glucocorticoids.

dexamethasone: *See glucocorticoids.*

diabetes: Type 1 (juvenile) diabetes is an autoimmune disorder in which the pancreas is unable to secrete insulin. Type 2 (adult-onset; a.k.a. insulin-resistant) diabetes is a disorder, typically brought on by obesity, in which cells throughout the body have become resistant to the effects of insulin.

dopamine: A type of neurotransmitter whose numerous functions include a role in anticipation of pleasure; abnormalities in it have been found in individuals with depression.

epinephrine: A hormone released during times of stress by the adrenal glands under the control of the sympathetic nervous system; it is also known as adrenaline. Epinephrine plays a key role in virtually all aspects of the stress-response.

fetal origins of adult disease (FOAD): This is an emerging concept in medicine, focusing on the fact that events during fetal life can program lifelong aspects of bodily function. As the example covered most in this course, fetal malnutrition often causes increased insulin secretion throughout life.

follicle-stimulating hormone (FSH): A pituitary hormone that stimulates follicle maturation in females and sperm maturation in males.

frontal cortex: The brain region involved in decision making, impulse control, long-term planning, and gratification postponement.

glucagon: A hormone released from the pancreas during stress that helps mobilize energy from storage sites in the body.

glucocorticoid: Any of a class of hormones released from the adrenal gland during stress that play a key role in virtually all facets of the stress-response. The primate/human version is cortisol, also known as hydrocortisone. Synthetic versions often prescribed by physicians include dexamethasone and prednisone.

gluteal fat: Fat deposits around the buttocks.

glycogen: The storage form of glucose/carbohydrates in the body.

Helicobacter pylori: A bacteria that causes a large percentage of cases of peptic ulcer. Chronic stress can impair the ability of the body to repair such ulcers.

hippocampus: A part of the brain's limbic system that is centrally involved in learning and memory and highly sensitive to the effects of stress.

homeostasis: A state of equilibrium, with physiological endpoints functioning in an optimal range.

hormone: A chemical messenger released by glands into the bloodstream, where it travels and has effects elsewhere in the body.

hydrocortisone: *See glucocorticoids.*

hyperalgesia: Exaggerated pain sensitivity.

hyperglycemia: Elevated blood-sugar (glucose) levels.

insulin: A hormone released from the pancreas that promotes the storage of glucose throughout the body. It is normally secreted when blood glucose levels rise; secretion is inhibited in the early phases of the stress-response.

John Henryism: A personality style where one perceives oneself to have control over circumstances where, in fact, that is not the case. It has been specifically applied to working-class African Americans and is associated with a greatly increased risk of cardiovascular disease.

learned helplessness: A term often used in the context of depression, describing a state where an individual, due to repeated psychological stress, has lost the capacity to recognize circumstances where it is possible to effectively cope with a stressor.

limbic system: A region of the brain that plays a central role in emotion.

long-term potentiation (LTP): An increase in the ease with which neurons communicate with each other across synapses; this increase in excitability is thought to be a cellular building block of memory formation.

luteinizing hormone (LH): A pituitary hormone that stimulates estrogen synthesis in females and testosterone synthesis in males.

metabolic syndrome: An emerging concept in medicine focusing on the fact that there is often overlap between the causes and symptoms of cardiovascular disease and of metabolic diseases such as diabetes; the syndrome refers to a constellation of symptoms that can include hypertension, obesity, hyperglycemia, and insulin resistance.

neurogenesis: The generation of new neurons. The fact that this can occur in the adult brain has been a revolution in neurobiology.

neurotransmitter: A chemical messenger with which one neuron communicates with another. Examples include serotonin, dopamine, and norepinephrine.

norepinephrine (a.k.a. **noradrenaline**): A type of neurotransmitter closely related to epinephrine. There is good evidence that its release in one region of the brain is blunted in depression; in a different part of the nervous system, it plays a central role in the sympathetic nervous system (along with epinephrine).

parasympathetic nervous system: *See* **autonomic nervous system**.

post-traumatic stress disorder (PTSD): A psychiatric disorder comprising a constellation of symptoms (e.g., sleep disruption, flashbacks, and hypersensitivity to stimuli) caused by severe trauma (e.g., combat trauma, childhood abuse, or rape).

prednisone: *See* **glucocorticoids**.

prolactin: A hormone released from the pituitary gland in response to stress, exercise, and nursing. It inhibits aspects of reproductive physiology.

psychogenic: Generated by psychological factors.

psychomotor retardation: A key symptom of major depression, in which thought and action seem exhausting.

rapid eye movement (REM) sleep: The sleep state during which dreaming occurs. It unexpectedly involves higher levels of activity in some brain regions than during normal waking.

receptor: A hormone or neurotransmitter carrying messages from one cell to another. Each type of hormone or neurotransmitter binds to a specific receptor on a target cell and exerts its actions through that route (e.g., estrogen stimulates uterine growth by binding to estrogen receptors in uterine cells).

selective serotonin reuptake inhibitor (SSRI): Any of a class of antidepressants (e.g., Prozac) that increase serotonin signaling in the synapse by blocking their reuptake (i.e., removal) from the synapse.

serotonin: A type of neurotransmitter. Of greatest relevance, evidence suggests that a shortage of serotonin in some brain regions contributes to depression.

slow-wave sleep: The deepest stage of sleep, in which the most energy restoration occurs. This is the sleep stage most disrupted by stress.

socioeconomic status (SES): An aggregate measure that incorporates level of education, wealth, and place of residence. Low SES is a predictor of increased risk for a wide variety of disease, as well as for significantly shortened life expectancy.

steroids: A class of structurally related hormones. For the purpose of this course, the most important ones are glucocorticoids, estrogen, progesterone, and testosterone.

stress dwarfism (a.k.a. psychogenic dwarfism, psychosocial dwarfism): A disorder in which growth in a child is significantly impaired by severe psychological stress.

stressor: An external perturbation that disrupts homeostasis; also, the psychological anticipation of such a perturbation occurring.

stress-response: The array of hormonal and neural adaptations in the body meant to reestablish homeostasis.

sympathetic nervous system: *See autonomic nervous system.*

synapse: The microscopic gap between the branches of two neurons; excitation in one neuron leads to the release of specific neurotransmitters, which float across the synapse, bind to specialized receptors, and alter the function of the other neuron.

thyroid hormone: Secreted by the thyroid gland, its main function is to increase metabolism. Abnormally low thyroid hormone levels (i.e., hypothyroidism) can give rise to depression.

toxic hostility: A personality style where an individual consistently interprets benign events as being threatening and calling for a hostile coping response. This modern incarnation of the type A personality concept carries an increased risk of cardiovascular disease.

triglycerides: The storage form of fats.

type A personality: A personality style first described in the 1950s that carries an increased risk of cardiovascular disease. In its original formulation, type A individuals tend to be highly competitive, overachieving, time-pressured, impatient, and hostile. *See also toxic hostility.*

ulcer: An area of tissue erosion (e.g., on skin or on the stomach lining).

Bibliography

Adam, T., and E. Epel. "Stress, Eating and the Reward System." *Physiology and Behavior* 91 (2007): 449.

Arnsten, A. "Stress Signaling Pathways That Impair Prefrontal Cortex Structure and Function." *Nature Reviews Neuroscience* 10 (2009): 410.

Bangasser, D., and T. Shors. "Critical Brain Circuits at the Intersection between Stress and Learning." *Neuroscience and Biobehavioral Reviews* (forthcoming).

Blum, D. *Love at Goon Park: Harry Harlow and the Science of Affection*. New York: Berkeley, 2004.

Burke, K., T. Franz, D. Miller, and G. Schoenbaum. "The Role of the Orbitofrontal Cortex in the Pursuit of Happiness and More Specific Rewards." *Nature* 454 (2008): 340.

Caudill, M. *Managing Pain Before It Manages You*. 3rd ed. New York: Guilford Press, 2008.

Cohen, S., D. Janicki-Deverts, and G. Miller. "Psychological Stress and Disease." *Journal of the American Medical Association* 298 (2007): 1685.

Creswell, J., W. Welch, S. Taylor, D. Sherman, T. Gruenewald, and T. Mann. "Affirmation of Personal Values Buffers Neuroendocrine and Psychological Stress Responses." *Psychological Science* 16 (2005): 846.

Dallman, M., S. la Fleur, N. Pecoraro, F. Gomez, H. Houshyar, and S. Akana. "Glucocorticoids—Food Intake, Abdominal Obesity, and Wealthy Nations in 2004." *Endocrinology* 145 (2004): 2633.

Dement, W. *The Promise of Sleep*. New York: Dell, 2000.

Depp, C., I. Vahia, and D. Jeste. "Successful Aging: Focus on Cognitive and Emotional Health." *Annual Review of Clinical Psychology* 6 (2010): 527–550.

Gillespie, C., and C. Nemeroff. "CRF and the Psychobiology of Early-Life Stress." *Current Directions in Psychological Sciences* 16 (2007): 85.

Godfrey, K., and D. Barker. "Fetal Programming and Adult Health." *Public Health and Nutrition* 4 (2001): 611.

Kiecolt-Glaser, J., L. McGuire, T. Robles, and R. Glaser. "Emotions, Morbidity, and Mortality: New Perspectives from Psychoneuroimmunology." *Annual Review of Psychology* 53 (2002): 83.

Kim, J., and D. Diamond. "The Stressed Hippocampus, Synaptic Plasticity and Lost Memories." *Nature Reviews Neuroscience* 3 (2002): 453.

Kirkwood, T. "Healthy Old Age." *Nature* 455 (2008): 739.

Kleinman, A. "Culture and Depression." *New England Journal of Medicine* 351 (2004): 951.

Lue, T. "Erectile Dysfunction." *New England Journal of Medicine* 342 (2000): 1802.

Lupien, S., B. S. McEwen, M. R. Gunnar, and C. Heim. "Effects of Stress throughout the Lifespan on the Brain, Behaviour and Cognition." *Nature Reviews Neuroscience* 10 (2009): 434.

Marmot, M. *The Status Syndrome: How Social Standing Affects Our Health and Longevity*. New York: Henry Holt, 2005.

McEwen, B. "Protective and Damaging Effects of Stress Mediators." *New England Journal of Medicine* 338 (1998): 171.

Meerlo, P., R. E. Mistlberger, B. L. Jacobs, H. C. Heller, and D. McGinty. "New Neurons in the Adult Brain: The Role of Sleep and Consequences of Sleep Loss." *Sleep Medicine Reviews* 13 (2009): 187.

Monat, A., and R. Lazarus. *The Praeger Handbook on Stress and Coping*. Westport, CT: Praeger Press, 2007.

Morgan, D., K. A. Grant, H. D. Gage, R. H. Mach, J. R. Kaplan, O. Prioleau, S. H. Nader, N. Buchheimer, R. L. Ehrenkauf, and M. A. Nader. "Social Dominance in Monkeys: Dopamine D2 Receptors and Cocaine Self-Administration." *Nature Neuroscience* 5 (2002): 169–174.

Nestler, E., and R. Malenka. "The Addicted Brain." *Scientific American*, March 2004, 78.

Rubin, A. *Diabetes for Dummies*. 3rd ed. New York: Hungry Minds, 2008.

Sapolsky, R. M. *Why Zebras Don't Get Ulcers: A Guide to Stress, Stress-Related Diseases, and Coping*. 3rd ed. New York: Henry Holt, 2004.

Sapolsky, R. M., and J. Wingfield. "Reproduction and Resistance to Stress: When and How." *Journal of Neuroendocrinology* 15 (2003): 711.

Schwartz, B. "The Tyranny of Choice." *Scientific American*, April 2004, 71.

Selye, H. *The Stress of My Life*. New York: Van Nostrand, 1979.

Stansfeld, S., and M. Marmot. *Stress and the Heart: Psychosocial Pathways to Coronary Heart Disease*. London: BMJ Publishing, 2002.

Sternberg, E. *The Balance Within: The Science Connecting Health and Emotions*. New York: W. H. Freeman, 2001.

Taylor, S., L. Klein, B. Lewis, T. Gruenewald, R. Gurung, and J. Updegraff. "Biobehavioral Responses to Stress in Females: Tend-and-Befriend, Not Fight-or-Flight." *Psychological Reviews* 107 (2000): 411.

Tilbrook, A., A. I. Turner, and I. J. Clarke. "Effects of Stress on Reproduction in Non-Rodent Mammals: The Role of Glucocorticoids and Sex Differences." *Reviews of Reproduction* 5 (2000): 105.